Influence of Scar on Left Ventricular Performance at the Onset of Myocardial Ischemia: Shock Versus Heart Failure

TIMOTHY J. REGAN, ANTHONY J. PASSANNANTE, MOHAMMAD I. KHAN, HENRY A. OLDEWURTEL, and MOHAN U. JESRANI

From the Department of Medicine, New Jersey College of Medicine and Dentistry, Newark, New Jersey 07103 and the T. J. White Cardiopulmonary Institute, Jersey City, New Jersey 07304

ABSTRACT Obstruction of a major branch of the left coronary artery in a previously normal ventricle is not usually associated with shock, experimentally or clinically. To examine the early hemodynamic alterations which may determine the course of ischemia when myocardial scar exists from previous infarction, 16 animals were successfully studied 9 wk after obstruction of the left circumflex artery. Acute ischemia during thrombus formation in the anterior descending artery of intact anesthetized dogs with scar was compared with animals undergoing the same procedure in the absence of scar (group 1). In the chronic animals, two types of hemodynamic responses were observed. Group 2 was characterized by heart failure usually persisting through 3 hr, and group 3 by a different ventricular volume response and rapidly developing shock. The weight of ischemic and scar areas were comparable and coronary blood flow (^{85}Kr method) to the ischemic site was reduced to a similar extent. Animals in groups 1 and 2 remained normotensive and had similar elevations of left ventricular end-diastolic volume (indicator dilution method) during the initial 60 min of ischemia. Group 2 had a significantly larger rise of end-diastolic pressure, presumably related to altered elastic properties associated with scar of subendocardial distribution.

Group 3 had a stroke volume decline that was not significantly greater than group 2 and both groups had an initial rise of peripheral vascular resistance. Despite a nearly fourfold increase of left ventricular end-diastolic pressure, there was a significant decline of left ventricular end-diastolic volume in group 3. This preceded the onset of hypotension in group 3, with arterial pressure declining to a greater extent than stroke volume, usually culminating in cardiac standstill. Group 3 was distinguished by the presence of transmural scar, which was postulated to influence contiguous ischemic tissue in diastole so as to diminish ventricular volume. By analogy with the hemodynamics of acute pericardial tamponade, a reflex pathway activated in the myocardium in response to reduced end-diastolic volume has been suggested as a mechanism for the arterial hypotension.

Received for publication 28 April 1970 and in revised form 12 November 1970.

INTRODUCTION

The hemodynamic basis for the development of hypotension and shock during acute myocardial ischemia remains unresolved. Myocardial infarction occurs almost exclusively in the left ventricle and left coronary artery occlusion in acute myocardial ischemia is generally located within 1–2 cm of the origin of the anterior descending or circumflex branches (1). Previous experience in the normal dog has indicated that the initial episode of myocardial ischemia after obstruction of a single main branch of the left coronary near its origin is not associated with substantial hemodynamic abnormality (2, 3) unless the left main coronary artery (4) or multiple small branches are occluded (5). Thus, experimental models employing a previously normal myocardium have required embolization of multiple coronary arteries to produce hypotension (6), which does not closely parallel the usual vascular abnormalities associated with clinical myocardial infarction (7). Further, there is evidence in man suggesting that cardiac decompensation or shock during myocardial ischemia is usually associated with previous abnormality of the myocardium (8, 9).

To explore the possibility that the myocardium with scar from previous infarction might be associated with hemodynamic alterations qualitatively different and more severe than during the first episode of myocardial ischemia, the following studies have been undertaken. Approximately 9 wk after obstruction of the left circumflex artery, the animal was anesthetized and hemodynamic studies were conducted during acute ischemia attending obstruction of the anterior descending vessel. Determination of ventricular volumes and pressures as well as myocardial blood flow were performed during the initial stages of ischemia before the onset of marked circulatory abnormality to assess those hemodynamic factors which are associated with the development of shock in contrast to those attending heart failure. In addition, previously normal animals were studied during acute myocardial ischemia.

METHODS

19 male mongrel dogs ranging from 21 to 26 kg, surviving a previous posterior apical infarction from thrombotic obstruction of the left circumflex artery an average of 9 wk previously, were active and well nourished at the time of study. They were anesthetized with 3 mg/kg of morphine and 12 mg/kg of Nembutal, and ventilated to maintain arterial oxygen saturation and pH. An electrode catheter was placed in the left anterior descending coronary artery for thrombus production in the intact dog (3). This technique usually results in complete obstruction as judged by angiography and post-mortem examination. The clearance of ^{85}Kr injected distal to the thrombus was thus a measure of collateral blood flow to the acute ischemic area. Evans blue dye was injected distal to the obstruction at the end of the experiment and the dyed tissue was weighed. This area and the excised scar were both related to total left ventricular weight.

Catheters were placed in the pulmonary artery, left ventricle, and root of the ascending aorta for cardiac output, and left ventricular volume determinations were made by the dye dilution technique using Indocyanine green (ICG), a Gilford Model 103-IR Densitometer (Gilford Instrument Labs, Inc., Oberlin, Ohio), and an infusion-withdrawal pump (from Harvard Apparatus Co., Millis, Mass.). Dye was injected into the pulmonary artery for output determinations and into the left ventricle for volume measurements (10), while blood was sampled continuously at the aortic root for densitometric readings.

In order to evaluate the applicability and accuracy of the dye dilution methods at the low levels of cardiac output encountered in these experiments, five animals were studied before and after the production of marked reduction of cardiac output. Thoracotomy was performed under general anesthesia and a Statham K-series, cuff-type, flow probe (Statham Instruments, Inc., Los Angeles, Calif.) was fitted snugly around the ascending aorta, distal to the coronary ostia. The connecting wires were brought out through the sutured thorax and connected to a Statham Model K-2000 Electromagnetic Flowmeter. The output of the flowmeter was conducted to a HRD-2 Integrator. The amplitude of the integrator amplifier output was taken as proportional to the area under the flow-velocity curve and equated to the stroke volume. This quantity, multiplied by the heart rate, was taken as a measure of cardiac output and compared to cardiac output determined by the conventional dye dilution technique. Flowmeter readings were taken just before and after paired determinations of cardiac output by dye dilution and averaged for comparison with the dye method. The flowmeter technique was calibrated by equating the integrated values with the initial determination by dye dilution before hypotension. Cardiac output was reduced in all animals after introduction of a balloon catheter (U. S. Catheter Co. & Instrument Corp., Glen Falls, N. Y.) into a femoral vein and passage to the inferior vena cava. Graded inflation of the balloon partially occluded the inferior vena cava, reducing venous return and cardiac output. After each increment of balloon volume, at least 10 minutes were allowed to elapse to obtain hemodynamic stability before stroke volume (flowmeter) or cardiac output (dye) measurements were recorded. The correlation coefficient for 20 paired determinations with cardiac output reduced from a mean of 1.9 liters/min to a range of 0.12–0.84 liter/min was 0.922, indicating that the indicator dilution method should be appropriate for this study. During myocardial ischemia, the duplicate cardiac output values had a correlation coefficient of 0.90.

The determination of left ventricular volume by dye dilution measurement has been shown to correlate with the angiographic determination (11, 12). Since sequential measurements of left ventricular volume by angiography may produce sustained depression of ventricular function in the abnormal heart (13), the indicator dilution method has been applied to the sequential measurement. Each determination was performed in duplicate by injection of 1 ml of green dye through a 50 cm multihole Goodale-Lubin No. 8 catheter, with the end located approximately in the apical half of the left ventricle. Duplicate determinations of ventricular volume by indicator dilution during development of shock were found to have a correlation coefficient of 0.82.

To evaluate the presence of mitral regurgitation 25 ml of Hypaque were injected into the left ventricular chamber after placement of a catheter, at least 60 min before the experiment was begun in most of the 12 animals. In none was angiographic dye observed on fluoroscopy to regurgitate through the mitral valve. After the induction of ischemia by anterior descending obstruction, a single bolus of Hypaque was infused after final determinations of cardiac output in five of eight animals in group 2 and three of eight animals in group 3. At this stage of ischemia, no evidence of mitral regurgitation was observed. The normal ventricular volumes by dye dilution in the control period and the reduced ventricular volume during ischemia in group 2 are compatible with these findings.

Standard and precordial electrocardiogram leads were monitored for evidence of injury potential and arrhythmias. Ventricular and femoral arterial pressures were measured through 50 cm 8F Goodale-Lubin catheters obtained from the U. S. Catheter & Instrument Corp., and connected directly to the P23Db Statham strain gauge transducers. The transducers were placed at mid-thoracic level and balanced for equal sensitivity. Photographic recordings were made on a multichannel oscilloscope recorder (Electronics for Medicine, Inc., White Plains, N. Y.).

A Goodale-Lubin catheter was placed in the coronary sinus at the level of the great cardiac vein and arteriovenous samples were collected. Since adequate venous samples were frequently not obtained during ischemia, only arterial values are reported. Arterial lactate (14), pyruvate (15), and free fatty acid (16) concentrations were determined. Plasma potassium was analyzed on a Beckman B spectrophotometer

TABLE I

Hemodynamic Changes during Initial Episode of Regional Myocardial Ischemia

	Heart rate		Mean aortic pressure		Coronary blood flow		Left ventricular end-diastolic Pressure		Left ventricular end-diastolic Volume		Stroke volume		Ejection fraction	
	C*	E‡	C	E	C	E	C	E	C	E	C	E	C	E
	beats/min		*mm Hg*		*ml/100 g per min*		*mm Hg*		*ml/kg*		*ml/kg*			
Mean	142.7	140.7	119.8	113.0	96.0	26.8	5.8	10.8	2.68	3.94	0.54	0.45	0.204	0.117
SE	±9.2	±5.6	±3.9	±5.7	±2.7	±1.1	±0.7	±1.1	±0.18	±0.33	±0.06	±0.04	±0.02	±0.01
t test C vs. E	NS		NS		<0.001		<0.01		<0.01		<0.02		<0.01	

* Control.

‡ Experimental values after 50–60 min of ischemia.

(Beckman Instruments, Inc., Fullerton, Calif.) with a flame attachment. Duplicate determinations for blood oxygen were performed by spectrophotometric assay (17). Arterial pH was determined on a Beckman meter at 37°C and hematocrit by the glass capillary method. Donor animals were used for 15-ml blood replacements after each sampling.

To compare the hemodynamic response to ischemia in animals with normal myocardium versus the groups with myocardial scar, six previously normal animals that successfully underwent acute thrombus formation in the left anterior descending artery without serious arrhythmias, were evaluated during ischemia as outlined above. Statistical comparisons were expressed as standard error and the Student *t* test was paired or nonpaired, as appropriate (18).

RESULTS

The development of acute ischemia in the previously normal animal (group 1) was associated with ST segment elevation in lead 1 and coronary blood flow was reduced from a mean of 96 ml to 26 ml/100 g per min without significant change in heart rate or systemic arterial pressure. During the 1st hour of ischemia, left ventricular end-diastolic pressure (LVEDP) and volume increased by 86 and 47%, respectively (Table I). Stroke volume declined an average of 11%, whereas mean aortic pressure and heart rate were not significantly altered.

All but three of the chronic animals prepared for study survived a sufficient period during the second ischemic episode for experimental observations. Of these three, two died of ventricular fibrillation shortly after the onset of ischemia and one died early in ischemia after Hypaque infusion.

Thrombus formation in the left anterior descending artery was associated with substantial reduction of coronary blood flow and produced elevation of the ST segment in standard lead 1 in all 16 of the chronic animals reported. There were, however, two distinguishing patterns of hemodynamic behavior observed. One, characterized by heart failure and normotension, usually persistent through 3 hr of observation, was representative of animals in group 2. Group 3 animals exhibited hypotension which progressed to shock. Before the ischemic episide, the control heart rate, arterial and ventricular pressures, and stroke volume (Tables I, II, and III) did not differ significantly. The average ejection fractions were almost the same in groups 1 and 3 and the somewhat higher mean in group 2 was not significant, due to an overlap with half of the animals in group 3. During obstruction of the anterior descending artery, coronary blood flow was reduced a similar extent. In group 2, coronary flow declined from 98 to 25 ml/100 g per min, while in group 3, the reduction was from 92 to 22 ml/100 g per min.

During the second ischemic episode, there were substantial increases of left ventricular end-diastolic pressure and volume in the animals of group 2 which became maximal by 45–60 min of ischemia (Table II, Fig. 1). These parameters rose progressively during the early stages of ischemia and appeared to reach a plateau. There was an early reduction of stroke volume which did not appreciably decline therafter, in association with increases of end-diastolic pressure and volume. Heart rate did not change and there was a small nonsignificant decline of mean aortic pressure. Calculated peripheral resistance rose from 60 to 81 U, derived from the ratio of mean arterial pressure and cardiac output.

Six of eight group 2 animals survived the 3 hr of observation, although ventricular ectopic activity was usually present intermittently. The other two animals had ventricular fibrillation after 95 and 128 min of ischemia. There was no significant additional change of heart rate, aortic pressure, and LVEDP in the survivors after the initial hour of ischemia. In two of the animals in which stroke volume and ventricular end-diastolic volume were measured, there was similarly no noteworthy change detected after the initial hour.

TABLE II

Hemodynamic Changes during Second Ischemic Episode in Heart Failure Group

Dog No.	Heart rate		Mean aortic pressure		Coronary blood flow		Left ventricular end-diastolic Pressure		Left ventricular end-diastolic Volume		Stroke volume		Ejection fraction	
	C*	E‡	C	E	C	E	C	E	C	E	C	E	C	E
	beats/min		*mm Hg*		*ml/100 g per min*		*mm Hg*		*ml/kg*		*ml/kg*			
1	140	125	140	105	87	25	11	35	2.87	3.17	0.370	0.167	0.230	0.117
2	97	145	135	100	129	22	8	16	3.06	3.88	0.765	0.357	0.250	0.0925
3	190	170	125	120	99	34	5	30	2.49	4.70	0.667	0.524	0.268	0.119
4	128	98	110	112	91	27	9	20	2.75	3.83	1.01	0.995	0.367	0.259
5	170	176	107	107	84	24	8	25	2.37	3.69	0.678	0.426	0.286	0.115
6	163	157	103	130	95	32	6	24	3.12	4.54	0.755	0.635	0.242	0.140
7	170	175	140	124	94	21	4	18	1.49	2.22	0.482	0.360	0.323	0.155
8	150	170	132	116	108	19	8	28	3.16	5.45	0.604	0.571	0.190	0.106
Mean	151	152	124	114	98	25.5	7.38	24.5	2.66	3.94	0.666	0.504	0.270	0.138
SE	±10.3	±9.9	±5.4	±3.6	±5.1	±1.9	±0.80	±2.3	±0.20	±0.35	±0.07	±0.08	±0.02	±0.02
t test														
C vs. E	NS		NS		<0.001		<0.01		<0.01		<0.01		<0.01	
C vs. C§														
t	0.390		0.848		0.807		0.393		0.278		1.426		2.110	
P	NS		NS		NS		NS		NS		NS		NS	

* Control.

‡ Experimental values after 50–60 min of ischemia.

§ Controls in heart failure and shock groups compared.

The hemodynamic changes in the eight animals of group 3 are indicated in Table III and Fig. 2. The experimental values in Table III are those obtained before substantial fall in aortic pressure and the systemic pressure was similar to that of group 2. In spite of a nearly fourfold increase of LVEDP, there was a significant decline of left ventricular end-diastolic volume in this group, which was associated with a substantial

TABLE III

Hemodynamic Changes during Second Ischemic Episode in Shock Group

Dog No.	Heart rate		Mean aortic pressure		Coronary blood flow		Left ventricular end-diastolic Pressure		Left ventricular end-diastolic Volume		Stroke volume		Ejection fraction	
	C*	E‡	C	E	C	E	C	E	C	E	C	E	C	E
	beats/min		*mm Hg*		*ml/100 g per min*		*mm Hg*		*ml/kg*		*ml/kg*			
9	148	90	135	115	110	10	12	42	3.65	2.38	0.989	0.552	0.271	0.233
10	180	175	115	105	65	24	5	30	2.18	1.75	0.359	0.231	0.164	0.132
11	180	165	130	110	91	30	5	25	3.14	2.54	0.520	0.430	0.158	0.170
12	100	100	96	95	103	28	6	18	2.58	1.64	0.565	0.255	0.219	0.156
13	75	97	110	103	95	31	7	29	2.79	1.76	0.358	0.201	0.128	0.114
14	190	150	121	132	89	25	3	23	2.37	2.19	0.236	0.207	0.092	0.091
15	140	150	132	94	108	17	8	21	3.26	1.85	0.591	0.234	0.190	0.125
16	140	150	103	98	78	16	9	27	1.97	1.07	0.513	0.217	0.350	0.203
Mean	144.1	134.6	117.8	106.5	92.4	22.6	6.9	26.9	2.74	1.90	0.516	0.290	0.197	0.153
SE	±14.3	±11.9	±5.0	±4.5	±5.4	±2.7	±1.0	±2.6	±0.20	±0.16	±0.08	±0.045	±0.03	±0.02
t test														
C vs. E	NS		NS		<0.01		<0.01		<0.01		<0.01		<0.05	
t test of change in group 2 vs. group 3	NS		NS		NS		NS		<0.01		NS		<0.01	

* Control.

‡ Experimental values after an average of 50 min of ischemia but before development of progressive hypotension.

reduction of stroke volume. In the prehypotensive stage of ischemia, the peripheral resistance of these animals had risen from a control of 74 to 112 peripheral resistance units. The stroke volume decline was not significantly greater than that of group 2, and there was a lesser reduction of ejection fraction.

This stage of ischemia was maintained for a period ranging from 10 to 90 min in group 3, before arterial pressure began to progressively decline below a mean of 70 mm Hg. This plateau phase for the individual animals numbered 9 to 16 on Table III, lasted 57, 10, 70, 53, 62, 48, 90, and 64 min. Three of the animals had stroke volume measurements during the period of shock, which further declined an average of 20% below the lowest prehypotensive value. Calculated peripheral resistance at this time had fallen to approximately control levels. Left ventricular end-diastolic pressure during hypotension diminished by 6–13 mm Hg, presumably due to a reduction of afterload and venous return. Within 3–30 min after mean aortic pressure had declined below 55 mm Hg, all animals succumbed. Seven of the group had cardiac arrest after a period of bradycardia and prolongation of the QRS, and there was only a single episode of ventricular fibrillation.

Table IV indicates that only minor changes in arterial concentrations of lactate, pyruvate, potassium, hematocrit, pH, and arterial oxygen saturation occurred. There was no significant difference between groups in these responses to ischemia. However, arterial free fatty acid concentrations which increased in group 1 were significantly diminished in groups 2 and 3.

The size of the left ventricular area involved in the acute ischemic process was not significantly different in the two groups and the percentage of left ventricle involved by scar was similar (Table V). However, group 2 had a broader area of endocardial scar, involving the distal posterior papillary muscle and adjacent free wall of the left ventricle. Sequential cross-sections of this tissue revealed scar that usually penetrated no more than 2 mm of the inner wall, with only rare extension into the middle third of myocardium. The epicardial layer was uniformly free of scar. In group 3, a firm, fibrous scar extended through and through, from the endocardium to

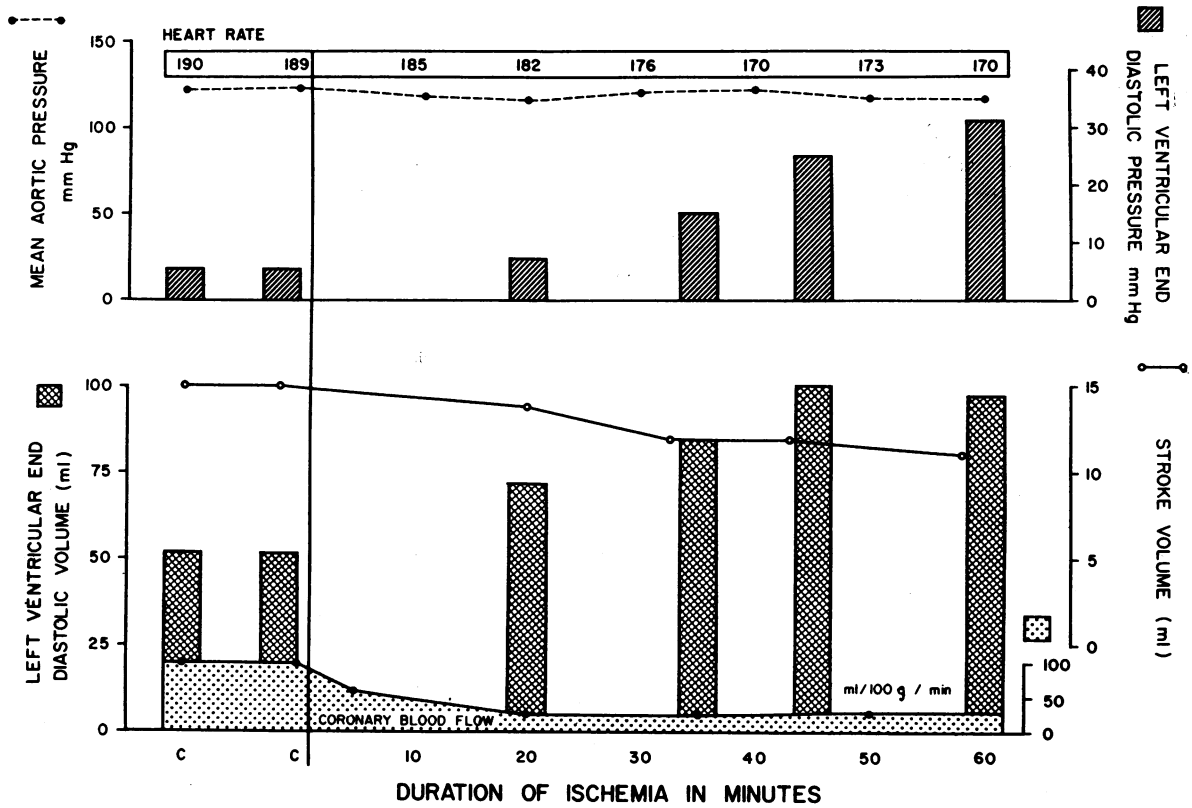

FIGURE 1 This is a representative animal illustrating the course of hemodynamic events in animals of group 2 characterized by a cardiac failure response to ischemia. After coronary blood flow was reduced to approximately one-third of control, a progressive rise of ventricular end-diastolic pressure and volume occurred associated with a moderate decline of stroke volume, which plateaued by 1 hr. Arterial pressure was maintained during this period and through the subsequent 3 hr of observation.

epicardium, but the extent of the endocardial fibrosis was less than in group 2.

DISCUSSION

The closed chest technique used to produce myocardial scar in these animals entailed thrombotic obstruction of the coronary artery. Absorption of the original thrombus in the circumflex artery was largely accomplished after an average of 9 wk, in agreement with a prior study (19). The collateral blood flow derived from the previously thrombosed circumflex artery during complete obstruction of the anterior descending vessel was apparently unimpeded, since the coronary blood flow levels to the ischemic site were similar to those observed without prior circumflex artery obstruction. In addition, the period between the initial infarction and the second ischemic episode, averaging over 9 wk, was sufficient to permit maturation of scar (20).

The observation of a reduced ventricular end-diastolic volume before the development of shock in group 3, clearly contrasts with the response of animals who did not become hypotensive. Since the measurement of left ventricular volume is crucial to this conclusion, a consideration of the validity of the indicator dilution measurement is in order. The in vivo validation of this technique has been based on a comparison with angiographic data. Two studies have revealed a close correlation of the two methods (11, 12); however, the indicator dilution method did give slightly higher estimates of end-diastolic volume. This has been attributed to the inclusion of a small fraction of blood at the indicator sampling site just distal to the aortic valve or alternatively, to a rapid increase in the ejection fraction after injection of angiographic dye. While a mixing problem may be more evident when volumes substantially deviate from normal, these two studies found a good agreement between both methods over a range of values. This included values only one-third of normal, which represent a greater reduction than observed with animals of group 3. It is of note that the indicator dilution method does reflect reduced ventricular volume in a disease state known to be associated with a small ventricle, isolated mitral stenosis

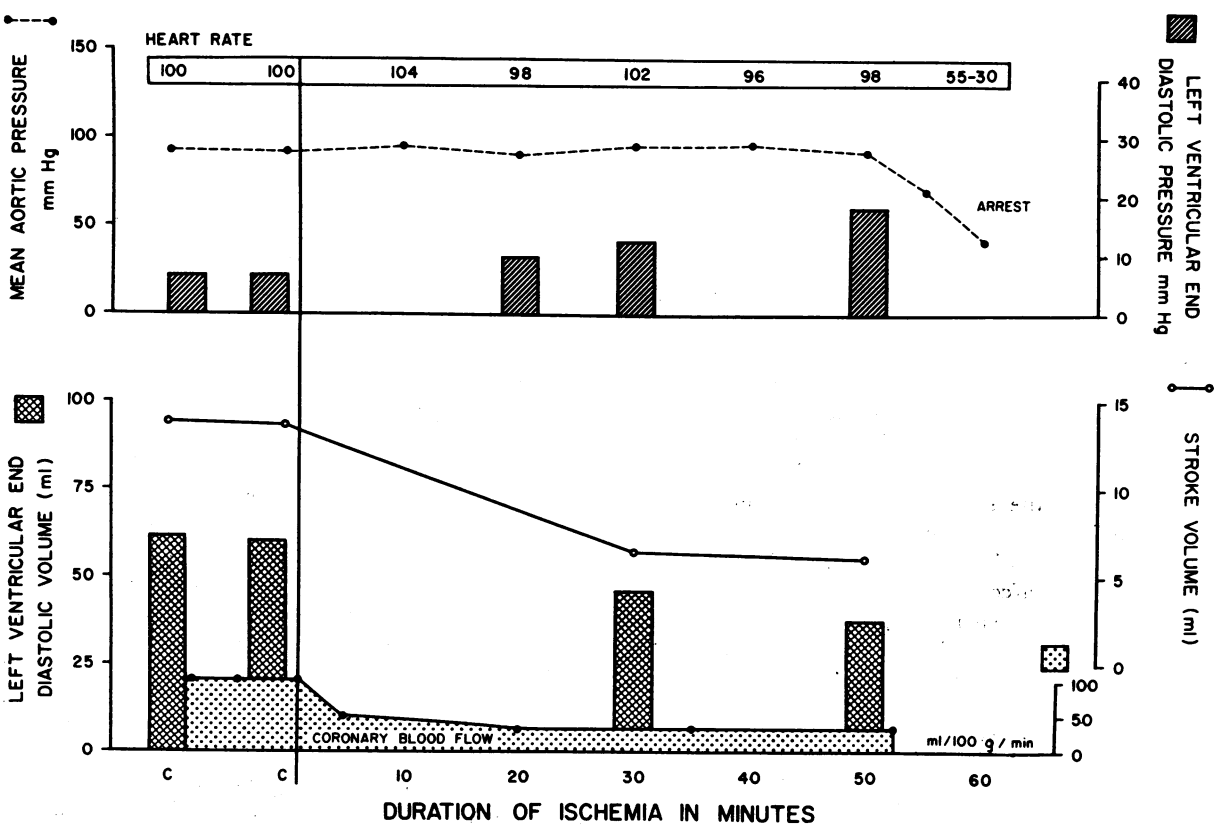

FIGURE 2 This is a representative animal of group 3, characterized by development of shock. After coronary blood flow was reduced to less than a third of control, a progressive rise of left ventricular end-diastolic pressure occurred, but end-diastolic volume declined, associated with a decrease in stroke volume. Despite these hemodynamic changes, arterial pressure was maintained for the initial 50 min of ischemia. Subsequently, arterial pressure progressively declined, associated with bradycardia and the development of cardiac standstill.

TABLE IV
Arterial Metabolites during Ischemia

Group...	1			2			3		
	C*	E‡	(n)	C*	E‡	(n)	C*	E§	(n)
Lactate, *mmoles/liter*	1.13 ±0.09	1.59 ±0.97	6	0.94 ±0.05	1.12 ±0.06	8	0.95 ±0.06	1.43 ±0.08	8
Pyruvate, *mmole/liter*	0.29 ±0.01	0.27 ±0.009	6	0.14 ±0.008	0.11 ±0.006	8	0.17 ±0.009	0.18 ±0.007	8
Potassium, *mEq/liter*	4.14 ±0.23	4.37 ±0.14	6	4.31 ±0.95	4.73 ±0.28	7	4.45 ±0.19	4.55 ±0.23	8
Free fatty acid, *μEq/liter*	784 ±57	1216 ±82	5	720 ±66	350 ±41	6	788 ±80	483 ±39	7
pH	7.37 ±0.006	7.35 ±0.015	6	7.36 ±0.010	7.33 ±0.009	8	7.38 ±0.007	7.34 ±0.009	8
O_2 saturation, %	91 ±0.8	89 ±1.2	6	92 ±0.9	88 ±1.1	8	93 ±0.7	90 ±1.0	8
Hematocrit	46 ±1.4	48 ±1.7	6	45 ±1.6	45 ±1.3	8	47 ±1.7	48 ±1.9	8

n = number of animals.
* Control values just before ischemia.
‡ Values at 60 min of ischemia.
§ Last value during ischemia one to 7 min before hypotension began.

(10). Greater difficulty in the application of the indicator method to analysis of right ventricular volume has been demonstrated (21), presumably related to the different inflow patterns and chamber architecture, resulting in a greater potential for nonmixing of blood. Thus, it is concluded that the reduced left ventricular diastolic volume in group 3 and enhanced volume in groups 1 and 2, with duplicate values in good agreement, must represent real changes from their respective control states, particularly since the least favorable comparison of the indicator and angiographic measurements has indicated that both methods reflect the same direction of change during acute interventions (22).

In regard to the state of the myocardium in these animals, it is difficult to make precise inferences when abnormal tissue may be in series with normal muscle, but a summation of effects may be seen as operative. The most obvious hemodynamic difference between animals undergoing an initial episode of myocardial ischemia compared to a second episode in the presence of scar,

TABLE V
Size of Ischemic and Scar Areas

Group	Weeks from first ischemic episode	Per cent of left ventricle: Acute ischemic area	Per cent of left ventricle: Scar area	Survival rate
2	9.2 ±1.8	32 ±1.5	5.9 ±1.1	6/8
3	9.7 ±1.5	34 ±1.3	6.3 ±0.9	0/8

was the pronounced rise of ventricular end-diastolic pressure in the latter group, more than three times the control levels. During acute ischemia in the previously normal heart, the ventricular filling pressure would appear to reach peak levels about twice normal. The increment of end-diastolic volume was similar in groups 1 and 2, so that the presence of scar with a subendocardial distribution would appear to permit ventricular dilatation of similar extent as in muscle without scar. However, the alteration of elastic properties conferred by the presence of scar in heart muscle apparently has sufficient net influence on the ventricle during diastole to produce the larger elevation of filling pressure. The greater reduction of stroke volume in group 2 animals was presumably related to greater asynchrony of muscle contraction or a more extensive loss of contractile units.

While the ventricular diastolic volume increase was quite similar in groups 1 and 2, group 3 had a qualitative difference in response to the second ischemic episode that was particularly significant in its occurrence before the onset of shock. The transmural scar in the shock group was usually continuous with the acute ischemic area as outlined by Evans blue dye. This segment of scar tissue, acting in series with the acute ischemic muscle, presumably reduced the ability of the ischemic area to dilate as seen in the previously normal heart. The net effect of the transmural scar, then appeared to consist not only of limiting the distention occurring in the acute ischemia area, but through an action on normal or ischemic muscle, resulted in a sig-

nificant reduction of end-diastolic volume from control values.

There was a significantly greater reduction of stroke volume in groups 2 and 3 compared to group 1, but the mean values after the onset of ischemia in the heart failure and shock groups, did not differ significantly. The somewhat higher mean stroke volume in the heart failure group is largely attributable to high values in two animals of group 2, Nos. 4 and 6, while the data for the remaining animals of both groups shows overlap. Hence, it is difficult to assign a crucial role to this parameter in the production of shock. The lower values of cardiac output found clinically were observed after the onset of shock and may have been secondary since they were not shown to be present prior to reduction of arterial pressure (23, 24). Alternatively, these may represent shock of different pathogenesis. The fact that the quantity of abnormal myocardial tissue was not different in these two groups, which has also been observed in human autopsy studies (8), supports the view that the mass of abnormal myocardium is not the determinant of a course marked by hypotension rather than heart failure. Thus, the behavior of the myocardium during diastole rather than systole, would appear to be more closely related to the shock process.

The arterial pressure was at first maintained during ischemia by peripheral vasoconstriction, both in animals that later developed shock and in the heart failure group that remained normotensive. However, during the onset of shock, the decline of arterial pressure was in excess of the reduction in cardiac output and peripheral resistance had returned to control, a situation frequently encountered during shock in patients with myocardial infarction (24).

The composition of arterial blood would not appear to influence the initiation of shock under the circumstances of this study. There was a small decline of arterial oxygen saturation in both groups without a significant difference betwen them, apparently related to pulmonary congestion. Central blood volumes measured by the Hamilton method rose from 194 ±13 ml to 248 ±17 ml in the heart failure group ($n = 7$), and from 176 ±15 ml to 227 ±20 ml in the shock group ($n = 5$). After accounting for the left ventricular volume change, the central blood volume increment is comparable in both groups. Presumably, the pulmonary vasculature participates in this increment, since the mean pulmonary artery pressure was elevated at 60 min in group 2 to a mean of 25 ±1.3 mm Hg ($n = 5$) and to a mean of 27 ±1.6 mm Hg in group 3 ($n = 4$), before the onset of hypotension. Although total blood volume was not measured, there appears to be no a priori reason for a major change in the relatively short period up to the development of hypotension.

There was also no significant difference between groups 2 and 3 in arterial lactate, pyruvate, potassium, hematocrit, pH, or oxygen saturation. The reduction in concentration of the free fatty acid compared to group 1 may be due to the greater reduction of cardiac output, since adipose tissue blood flow reduction can impede the delivery of free fatty acid to the systemic circulation, when enhanced sympathetic activity would be expected to produce higher blood levels (25, 26).

The transition into the phase of arterial hypotension presumably required a reflex mechanism. The source for such a vasodepressor response during myocardial ischemia would not appear to be the coronary arteries (4), since the major coronary artery branch was similarly involved in the heart failure and shock groups and the coronary flow reduction was of equal extent. Acute increments of LVEDP and volume have been found experimentally to produce a vasodepressor response (27) but the absence of such a response in group 2 animals argues against this mechanism.

Since the decline of ventricular end-diastolic volume was the singular hemodynamic difference before the appearance of shock, this alteration may have a crucial role in the subsequent decline of arterial pressure. An analogous abnormality exists in acute pericardial tamponade (28). Moderate restriction of ventricular filling was associated with a reduced stroke volume and enhanced peripheral resistance, while a greater degree of tamponade resulted in a progressive fall of arterial pressure that was proportionately greater than the reduction of stroke volume. In the group 3 animals, bradycardia, QRS prolongation, and arrest was the usual course during progressive shock. In unpublished studies of pericardial tamponade with progressive decline of arterial pressure, a similar change in heart rate and conduction has been observed. Thus, the reduced ventricular end-diastolic volume associated with ischemia in the myocardium with preexistent transmural scar and during pericardial tamponade, may activate an afferent pathway from the epicardial pericardium or the ventricle itself to produce the observed course of events.

This animal model of shock during myocardial ischemia appears to simulate myocardial infarction in man, in that it is associated with prior abnormality of ventricular muscle (8, 9) and occurs after occlusion of a main branch of the left coronary artery (1). However, shock could occur in a different setting in the unusual instance of left main coronary artery occlusion without previous myocardial injury (4). Alteration of the myocardium by the process of ageing or hypertrophy, may also be associated with more pronounced hemodynamic abnormality during the first myocardial infarction without segmental scar. Localization of scar near the base of the heart may confer less influence on myocardial function during the episode of ischemia. In addition, lower

grades of acute ischemia could result in hypotension that is less severe, with a course less rapid in progression, than observed in these shock animals. Finally, the course of the heart failure group over a period of many hours or days might evolve preterminally into a hemodynamic state similar to that observed in the shock group.

Therapeutic approaches to the observed hemodynamic abnormality culminating in shock are underway. It would appear that therapeutic interventions such as diastolic augmentation, which has the potential for reducing ventricular volume, would not seem warranted in the presence of a ventricular volume that is already considerably reduced.

ACKNOWLEDGMENTS

We gratefully acknowledge the technical assistance of Mrs. Bess Jenkins and Miss Elaine Podell and the secretarial services rendered by Mrs. Anne Binetti.

This work was supported in part by NHI Research Grant No. HE 09914 and Graduate Training Grant No. HE 05510 and a grant from the Monmouth County Heart Association of New Jersey. Cardiogreen used in this study was generously supplied by Hynson, Westcott & Dunning, Inc., Baltimore, Md.

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