

# Effects of Increasing Left Ventricular Filling Pressure in Patients with Acute Myocardial Infarction

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**ABSTRACT** Left ventricular performance in 19 patients with acute myocardial infarction has been evaluated by measuring left ventricular response in terms of cardiac output, stroke volume, work, and power to progressive elevation of filling pressure accomplished by progressive expansion of blood volume with rapid infusion of low molecular weight dextran. Such infusion can elevate the cardiac output, stroke volume, work, and power and thus delineate the function of the left ventricle by Frank-Starling function curves. Left ventricular filling pressure in the range of 20–24 mm Hg was associated with the peak of the curves and when the filling pressure exceeded this range, the curves became flattened or decreased. An increase in cardiac output could be maintained for 4 or more hr. Patients with a flattened function curve had a high mortality in the ensuing 8 wk. The function curve showed improvement in myocardial function during the early convalescence. When left ventricular filling pressure is monitored directly or as pulmonary artery end-diastolic pressure, low molecular weight dextran provides a method for assessment of left ventricular function.

## INTRODUCTION

Relatively few studies of left ventricular filling pressure have been performed in patients with an acute myocardial infarction. Fluck, Valentine, Triester, Higgs, Reid, Steiner, and Mounsey (1) found elevation of pulmonary arterial pressure during the first two days following an acute myocardial infarction. Nixon (2), Nixon, Taylor, and Morton (3), and Kirby, McNicol, and Tattersfield (4) measured left atrial or left ventricular pressure in

patients with pulmonary edema or shock after acute myocardial infarction. Cohn, Khatri, and Hamosh (5) and Loeb, Gunnar, Pietras, and Tobin (6) monitored left ventricular pressure patients with shock following infarction. Rapaport and Scheinman (7) have estimated left ventricular filling pressure at the bedside from changes in pulmonary artery diastolic pressure. With the excessive mortality rates in heart failure and cardiogenic shock, left ventricular function in patients with an acute myocardial infarction is an area requiring further investigation.

Recognizing relative hypovolemia or redistribution of blood volume (8) as contributing to inadequate cardiac performance in acute myocardial infarction, several investigators have advocated blood volume expansion in the management of left ventricular power failure (2, 9–13). Infusion of dextran has been advocated for treating shock and (or) severe heart failure associated with an acute myocardial infarction (12, 14). Under these conditions expansion of the blood volume increases left ventricular diastolic volume and filling pressure and accordingly cardiac output is increased by the Frank-Starling mechanism. An elevation in cardiac output in acute infarction by this mechanism depends on the extent of myocardial damage to the left ventricle, alteration in ventricular distensibility, and the over-all response of viable and damaged myocardial fibers to stretch. Furthermore, the range of filling pressures over which this mechanism is operative in acute infarction has not previously been defined. In the present investigation response of cardiac output, stroke volume, work, and power to serial stepwise increases in filling pressure has been systematically studied in 19 patients with acute myocardial infarction.

## METHODS

In 19 patients who were admitted to the Myocardial Infarction Research Unit (MIRU) of the University Hospital with an acute myocardial infarction, left ventricular performance was studied by augmentation of left ventricular filling

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pressure by low molecular weight dextran (LMWD)<sup>1</sup> infusion. Volume augmentation was performed 2–18 hr after admission to the unit. This was 12 hr to 3 days after admission to the hospital for chest pain, arrhythmia, or systemic embolus. Two patients were referred to this institution approximately 2 wk after infarction, one (J. R.) for arrhythmia and one (C. N.) for femoral artery embolus, although the latter had another infarction after arrival.

The diagnosis of acute myocardial infarction was based on a history and clinical picture compatible with the diagnosis of myocardial infarction. The presence of pathologic Q waves in the electrocardiogram with evolutionary changes in ST and T waves, and serial enzyme changes in the presence of typical evolving electrocardiographic patterns were also required. Electrocardiographic interpretation followed the criteria of the World Health Organization (15).

The investigative protocol for patients with acute myocardial infarction had been approved by the Human Use Committee of this institution. The nature and risks of the procedure were explained to the patient and a responsible family member, and informed consent was obtained according to the principles expressed in the Declaration of Helsinki as endorsed by the American Society for Clinical Investigation, Inc. (16).

Before the study the majority of patients received 25–50 mg of promethazine hydrochloride<sup>2</sup> intramuscularly. Each patient was studied supine or 10–15° head elevation in his own intensive care bed equipped with a radiolucent top.<sup>3</sup> The bed top was turned 90° to the chassis which allowed access to the patient's torso by a fluoroscopic C arm.<sup>4</sup> Catheters were positioned with fluoroscopic control using an image intensifier. The pulmonary artery was catheterized using a radio-opaque woven Dacron Goodale-Lubin catheter (usually No. 7). Alternatively, a PE90 catheter was floated into the pulmonary artery without fluoroscopic control. Arterial catheterization was performed by the Seldinger technique from the right brachial or femoral artery. A radiolucent Teflon tube with an inner diameter of 0.97 mm and an outer diameter of 1.5 mm<sup>5</sup> was used in the brachial artery or a Teflon Gensini catheter in the right femoral artery. Under fluoroscopic control these were manipulated with the flexible wire guide retrograde into the central aorta or left ventricle. Left ventricular end-diastolic pressure was measured directly from a catheter positioned in the left ventricle or was estimated from the pulmonary artery end-diastolic pressure. In three patients both pressures were measured simultaneously before volume augmentation, and in another throughout LMWD infusion.

Strain gauges for recording pressure were mounted on a molded leucite saddle on the patient's arm or leg. The zero was marked on the chest 10 cm above the patient's back. The catheters were flushed carefully and frequently using 5% dextrose in water with 20 mg of heparin per liter. After insertion of the catheters, the patients were heparinized with 5000–7000 U of heparin intravenously. A constant infusion of 30–40 microdrops per minute of a heparinized solution was maintained through the pulmonary artery or venous catheter. The cardiac catheters remained in position

for 24–72 hr for hemodynamic monitoring and cardiac output measurements.

Cardiac outputs were performed by dye dilution technique with injection into the central venous or pulmonary artery catheter with sampling from the left ventricle or central aorta. Arterial blood for dye dilution cardiac output was drawn through a cuvette densitometer<sup>6</sup> and calculated by a special purpose analog cardiac output computer.<sup>7</sup> Calibration of the densitometer system for the indicator dilution cardiac outputs was meticulously performed using the same spring-loaded syringe in delivering dye for calibration that was used for dye injection into patients. This amount of dye was 4.5 mg; for calibration it was diluted to a concentration of 0.009 mg/ml (equal to 9 mg/liter). Densitometer deflection with this concentration was the calibration factor. Two concentrations, 4.5 mg/liter and 9 mg/liter were used in calibration to confirm the linearity of the densitometer on approximately every sixth patient. Clean dry pipettes were used for transferring diluted dye and blood for calibration. Calibration was performed daily if outputs were determined on more than 1 day. The cardiac output from the analog computer was confirmed by the semilogarithmic replot of the dye dilution curves and the cardiac output determined after integrating the area by the trapezoidal method. This was performed on approximately every fifth indicator dilution curve and the values obtained by the manual method were found to agree within  $5.8 \pm 3.5\%$  of that determined by the analog computer (17). All subjects were anticoagulated with heparin free of sodium bisulphite, as the latter compound has been reported to interfere with the stability of Indocyanine Green (18).

The left ventricular filling pressure was augmented by the rapid intravenous administration of LMWD with 50-ml syringes. After each 100–200 ml had been injected manually pressures and cardiac output were recorded: pressures within 30 sec and cardiac outputs within about 3–5 min. The total procedure, consisting of 200–800 ml dextran, serial pressure recordings, and cardiac outputs, was completed in 20–30 min. In six patients a second dextran infusion study was performed similarly 1–2 days after the initial study.

No patient had significant deviations of arterial blood hydrogen ion concentration when the dextran infusion was performed. No significant change in venous hematocrit occurred after LMWD infusion. Considering all studies, the hematocrit fall averaged 3 vol % on the 2 days after infusion with a range of –16 to +6 vol %. Only three patients had hematocrits falling below 30 (27, 26, and 23 respectively) within 2 days following infusion. The patient with the hematocrit falling to 23 developed a hematoma in the inguinal area requiring transfusion.

Complications of the study in these patients included hematoma formation around catheter insertion in the brachial artery and femoral vein requiring transfusion in a heparinized 64 yr old female (H. E.) (19). One patient (R. J.) developed dyspnea and wheezes on infusion of LMWD which responded immediately to phlebotomy. Two other patients (C. N. and O. B.) died of progressive heart failure on the 9th and 10th hospital day, 8 and 6 days after the volume augmentation respectively.

Data were displayed in the form of ventricular function curves. Cardiac output, stroke volume, stroke work, and

<sup>1</sup> Rheomacrodex (Dextran 40), Pharmacia Fine Chemicals, Inc., Piscataway, N. J.

<sup>2</sup> Phenergan, Wyeth Laboratories, Marietta, Pa.

<sup>3</sup> Eichenlaubs Contract Furniture, Pittsburgh, Pa.

<sup>4</sup> North American Phillips Co., New York.

<sup>5</sup> American Super-Temp Wires, Winooski, Vt., Teflon TTE19.

<sup>6</sup> Model No. 103 IR, Gilford Instrument Labs, Inc., Oberlin, Ohio.

<sup>7</sup> GAP/R Model SK-2V, Lexington Instruments Corp., Waltham, Mass.

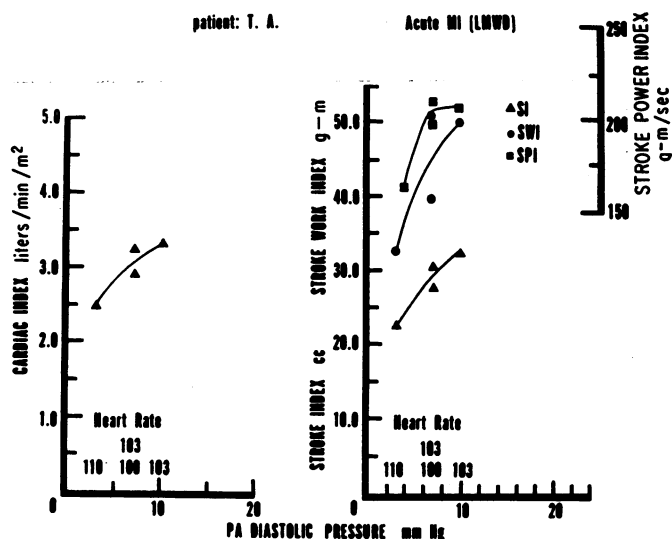


FIGURE 1 Left ventricular function curves in a patient with acute myocardial infarction. Left ventricular function curves relating cardiac index on the left and stroke work index, stroke power index on the right to left ventricular filling pressure as determined by pulmonary artery end-diastolic pressure. These parameters of left ventricular function rose as left ventricular filling pressure rose. The heart rate changed very little and is recorded below each point on the curve. The patient received 600 ml of dextran in 200-ml increments. MI = myocardial infarction; LMWD = low molecular weight dextran; PA = pulmonary artery.

stroke power corrected for body surface area were plotted as a function of pulmonary artery end-diastolic pressure or left ventricular end-diastolic pressure. Stroke volume was calculated in milliliters as cardiac output divided by heart rate. Stroke work (SW) was calculated as gram-meters by the formula:

$$\text{Stroke work} = \text{stroke volume} \times (\text{mean systolic pressure} - \text{left ventricular end-diastolic pressure}) \times 0.0136$$

and

$$\text{mean systolic pressure in mm Hg} = 0.8 (\text{aortic systolic} - \text{aortic diastolic pressure}) + \text{aortic diastolic pressure}^*$$

Stroke power = stroke work/duration of left ventricular ejection. Duration of ejection was determined from the aortic pressure pulse. When only left ventricular pressure was available: mean systolic pressure = 0.90 (left ventricular systolic pressure).<sup>9</sup>

\*This formula for mean systolic pressure was experimentally confirmed by planimetry of three aortic pulse wave forms in each of 11 instances in 10 patients. The calculated value correlated with the planimetric value for mean systolic pressure with a correlation coefficient of  $r = 0.994$  (20). The calculated value agreed with the planimetric value within  $2.9 \pm 2.9\%$  (17).

<sup>9</sup>The factor 0.90 was obtained experimentally in 11 instances on 10 patients with a recorded aortic pressure by relating the planimetrically determined mean systolic pressure to the peak aortic systolic pressure. The factor was necessary to calculate stroke work when only left ventricular pressure was available. The standard deviation of the mean from the factor of 0.90 was 0.009 (21).

The greatest slope of each stroke index-filling pressure curve was calculated as the change in stroke index from base line to maximum value and related to the respective change in filling pressure as the ratio  $\Delta \text{stroke index} / \Delta \text{filling pressure}$ . The added volume of LMWD ( $\Delta V$ ) was related to change in filling pressure ( $\Delta P$ ) by the ratio  $\Delta V / \Delta P$  as an estimate of the diastolic compliance of the left ventricle.

## RESULTS

The hemodynamic data in 19 patients with acute myocardial infarction before, at the maximal response, and after the period of volume augmentation are summarized in Table I. The complete data have been filed with the American Documentation Institute.

Patients were studied an average of 27 hr (range 6-72) after acute infarction. Following the rapid infusion of LMWD, the left ventricular filling pressure invariably rose in these patients with a concomitant rise in cardiac index. Since changes in heart rate during the infusions were minimal, the increase in stroke index paralleled that of cardiac index. Similarly, the stroke work and stroke power indices increased. (Figs. 1 and 2). Patient T. A. (Fig. 1) had undergone a spontaneous diuresis of 3550 ml in the preceding 20 hr and may have been relatively hypovolemic. His cardiac index rose from 2.5 to 3.3 liters/min per  $m^2$  with an increase in pulmonary artery diastolic pressure from 3 to 10 mm Hg.

TABLE I  
*Hemodynamic Data before, during, and after Volume Augmentation*

Patient	Diagnosis	Time of study, from probable onset of MI	LMWD added	PAEDP	LVP	AP	CI	SI	SWI	SPI	HR	RA
			cc	mmHg	mmHg	mmHg	liters/min per m <sup>2</sup>	cc	g-m	g-m/sec	beats/min	mm Hg
M. P.	ALMI	6 hours	Base line	13	—	$\frac{185}{88}$	1.7	21	44	137	83	—
			500 cc	29	—	$\frac{188}{93}$	2.3	25	48	150	92	—
			8 hr later	15	—	$\frac{172}{74}$	1.9	21	39	139	91	—
		52 hr	Base line	11	—	$\frac{152}{67}$	2.1	20	34	142	98	—
			500 cc	23	—	$\frac{163}{71}$	3.1	30	50	192	102	—
			2 hr later	9	—	$\frac{149}{64}$	2.9	30	50	192	98	—
			4 hr later	5	—	$\frac{143}{65}$	2.5	26	43	179	97	—
			6 hr later	—	—	$\frac{144}{64}$	2.7	28	46	178	98	—
			8 hr later	10	—	$\frac{137}{65}$	2.3	23	35	146	100	—
			10 hr later	6	—	$\frac{130}{60}$	2.0	22	30	125	93	—
G. McL.	DMI	20 hr	Base line	11	—	$\frac{133}{85}$	3.7	37	56	200	101	8
			800 cc	18	—	$\frac{134}{83}$	4.2	44	63	218	95	19
			2 hr later	12	—	$\frac{107}{68}$	3.3	50	59	236	85	12
			4 hr later	12	—	$\frac{119}{68}$	4.4	48	63	242	93	6
			6 hr later	—	—	$\frac{121}{79}$	3.7	42	—	—	87	12
		41 hr	Base line	7	—	$\frac{122}{77}$	3.7	39	56	216	95	13
			400 cc	14	—	$\frac{127}{78}$	4.2	43	60	222	98	13
			2 hr later	—	—	$\frac{116}{73}$	4.1	38	—	—	106	6
			4 hr later	13	—	$\frac{102}{66}$	3.9	41	46	177	94	9
			6 hr later	12	—	$\frac{109}{66}$	3.4	33	39	162	101	10
A. C.	ASMI	17 hr	Base line	14	—	$\frac{110}{69}$	2.2	28	35	129	76	—
			600 cc	27	—	$\frac{125}{75}$	3.4	37	44	157	92	—
			6 hr later	17	—	$\frac{117}{76}$	2.3	25	31	129	93	—
		65 hr	Base line	8	—	$\frac{109}{66}$	3.0	34	40	174	92	—
			600 cc	20	—	$\frac{117}{66}$	4.8	53	63	242	90	—
			2 hr later	11	—	$\frac{111}{67}$	4.0	49	63	262	81	—
			4 hr later	12	—	$\frac{109}{66}$	3.1	42	50	178	76	—
H. E.	DMI	7 hr	Base line	13	—	$\frac{133}{81}$	2.3	20	30	125	114	—
			400 cc	18	—	$\frac{152}{104}$	3.4	25	42	190	137	—

TABLE I—(Continued)

Patient	Diagnosis	Time of study, from probable onset of MI	LMWD added	PAEDP	LVP	AP	CI	SI	SWI	SPI	HR	RA
			cc	mmHg	mmHg	mmHg	liters/min per m <sup>2</sup>	cc	g-m	g-m/sec	beats/min	mm Hg
E. W.	ILMI	21 hr	Baseline	15	$\frac{177}{15}$	—	2.5	30	60	—	83	6
			400 cc	20	$\frac{183}{20}$	—	3.3	38	76	—	86	10
		43 hr	Base line	10	—	$\frac{124}{56}$	1.6	—	—	—	Irreg.	6
			700 cc	17	—	$\frac{166}{61}$	2.4	—	—	—	Irreg.	8
L. W.	AMI	3 days	Base line	5	—	$\frac{123}{77}$	2.1	24	36	156	88	—
			600 cc	26	—	$\frac{144}{89}$	2.9	28	41	171	103	—
			2 hr later	13	—	$\frac{128}{77}$	3.1	31	44	169	98	—
R. D.	ASMI	24 hr	Base line	29	—	$\frac{117}{80}$	2.4	21	23	127	108	—
			200 cc	39	—	$\frac{128}{88}$	2.8	26	29	145	108	—
			5 hr later	32	—	$\frac{124}{80}$	3.0	27	31	172	112	—
			13 hr later	26	—	$\frac{117}{72}$	3.0	28	31	155	108	—
		36 hr	Base line	24	—	$\frac{104}{68}$	2.8	28	28	140	99	—
			200 cc	33	—	$\frac{106}{69}$	3.0	29	26	118	103	—
O. B.	AMI	58 hr	Base line	10	—	$\frac{121}{97}$	1.0	9	13	65	106	—
			200 cc	29	—	$\frac{123}{97}$	1.1	11	13	68	103	—
			300 cc + Isoproterenol	33	—	$\frac{116}{91}$	1.2	12	13	65	103	—
			Norepinephrine	30	—	$\frac{111}{91}$	1.0	9	9	50	115	—
W. K.	AMI	12 hr	Base line	4	—	$\frac{166}{90}$	2.9	42	83	276	70	—
			600 cc	22	—	$\frac{194}{94}$	4.2	54	112	350	78	—
			2 hr later	20	—	$\frac{184}{95}$	3.9	50	99	310	78	—
			4 hr later	7	—	$\frac{172}{93}$	3.0	45	91	292	68	—
C. G.	ALMI	42 hr	Base line	—	$\frac{134}{25}$	—	3.1	32	42	—	99	—
			250 cc	—	$\frac{145}{30}$	—	3.7	36	50	—	102	—
M. Ps.	DMI	48 hr	Base line	—	$\frac{106}{20}$	—	2.1	23	24	—	91	6
			300 cc	—	$\frac{114}{24}$	—	2.4	26	28	—	92	7
L. B.	DMI	42 hr	Base line	16	—	$\frac{127}{84}$	2.6	30	42	191	85	—
			400 cc	21	—	$\frac{137}{93}$	3.5	36	52	226	97	—
		59 hr	Base line	11	—	$\frac{126}{87}$	2.3	25	36	164	93	—
			600 cc	21	—	$\frac{121}{80}$	3.0	31	39	169	96	—

TABLE I—(Continued)

Patient	Diagnosis	Time of study, from probable onset of MI	LMWD added	PAEDP	LVP	AP	CI	SI	SWI	SPI	HR	RA
			cc	mmHg	mmHg	mmHg	liters/min per m <sup>2</sup>	cc	g-m	g-m/sec	beats/min	mm Hg
T. A.	AMI	19 hr	Base line	3	—	$\frac{117}{76}$	2.5	23	33	165	110	—
			600 cc	10	—	$\frac{137}{79}$	3.3	32	50	208	103	—
J. R.	ALMI	17 days	Base line	—	$\frac{95}{8}$	—	4.0	37	39	—	107	10
			400 cc	—	$\frac{110}{17}$	—	5.6	53	60	—	105	16
R. J.	AMI	48 hr	Base line	14	—	$\frac{96}{76}$	1.5	16	17	85	90	—
			400 cc	23	—	$\frac{105}{83}$	1.2	15	16	80	80	—
			Phlebotomy 300 cc	18	—	—	1.6	20	—	—	80	—
E. D.	DMI	18 hr	Base line	18	—	$\frac{104}{59}$	2.8	31	25	109	89	—
			600 cc	29	—	$\frac{115}{70}$	3.4	36	38	181	95	—
R. M.	ALMI	21 hr	Base line	12	—	$\frac{107}{55}$	2.8	35	41	—	80	—
			600 cc	26	—	—	2.8	37	—	—	75	—
			Phlebotomy 200 cc	26	—	—	2.8	29	—	—	94	—
L. C.	AMI	6 hr	Base line	—	$\frac{78}{18}$	—	2.3	16	12	—	149	—
			400 cc	—	$\frac{85}{26}$	—	3.1	25	17	—	124	—
C. N.	ALMI	11 hr	Base line	22	—	$\frac{125}{95}$	1.6	12	16	89	133	—
			200 cc	36	—	$\frac{129}{95}$	2.1	17	20	111	129	—

Irreg. = irregular; AMI = anterior myocardial infarction; DMI = diaphragmatic myocardial infarction; ALMI = anterolateral myocardial infarction; ASMI = antero-septal myocardial infarction; ILMI = inferolateral myocardial infarction; LMWD = low molecular weight dextran; PAEDP = pulmonary artery end-diastolic pressure; LVP = left ventricular pressure; AP = aortic pressure; CI = cardiac index; SI = stroke index; SWI = stroke work index; SPI = stroke power index; HR = heart rate.

Two other patients may also have been relatively hypovolemic as judged by pulmonary artery end-diastolic pressures of 4 (W. K.) and 5 mm Hg (L. W.). The cardiac index of patient W. K. rose from 2.9 to 4.2 liters/min per m<sup>2</sup> with an increase in pulmonary artery end-diastolic pressure from 4 to 22 mm Hg, while the cardiac index of patient L. W. rose from 2.1 to 2.9 liters/min per m<sup>2</sup> with an increase in pulmonary artery end-diastolic pressure from 5 to 26 mm Hg. Each of these three patients received 600 ml of dextran infusion.

Patient J. R. (Fig. 2) realized an increase in cardiac index from 4.0 to 5.6 liters/min per m<sup>2</sup> for an elevation of left ventricular end-diastolic pressure from 8 to 17 mm Hg. Such an increase in cardiac index did not always follow a rise in left ventricular filling pressure (Fig. 3). Patient O. B. (Fig. 3) obtained no increase in cardiac

index with volume augmentation, nor did she with norepinephrine or isoproterenol infusion after the volume.

In most patients the stroke index rose briskly for an increase in filling pressure. The resultant increase in stroke index per mm Hg elevation in filling pressure was 1.0 cc or greater in 10 curves. However this ratio,  $\Delta$  stroke index/ $\Delta$  filling pressure, was 0.30 cc/mm Hg or greater in 20 function curves. The mean ratio for these function curves was  $1.06 \pm 0.56$  cc/mm Hg (17). All these patients survived hospitalization. None of these patients were in congestive failure except one (L. C.) who had been in pulmonary edema within the hour requiring phlebotomy. In five patients the function curves relating stroke index to filling pressure were depressed or flattened. In this group of patients the ratio,  $\Delta$  stroke index/ $\Delta$  filling pressure was less than 0.30 cc/mm Hg

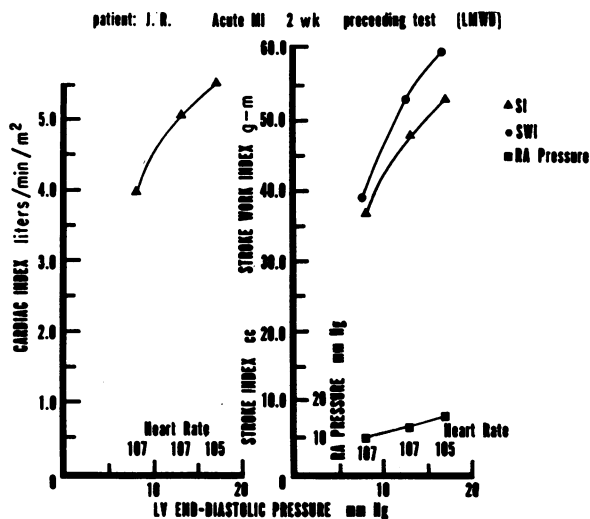


FIGURE 2 Left ventricular function curves in a patient with acute myocardial infarction. Left ventricular function curves relating cardiac index, stroke index, stroke work index, and stroke power index to left ventricular end-diastolic pressure. This patient received 400 ml dextran in 200-ml increments. See legend for Fig. 1. Right atrial pressure rose concomitantly with left ventricular end-diastolic pressure. LV = left ventricular; RA = right atrial.

indicating little or no increment in stroke volume despite elevation of filling pressure. The mean ratio for these five function curves was  $0.20 \pm 0.07$  cc/mm Hg (17). There was a statistically significant difference in the means of the two groups of curves using the Student *t* test ( $P < 0.001$ ) (22). Four of these patients were in incipient congestive heart failure as evidenced by a ventricular gallop, rales during infusion, or having been in frank congestive heart failure within hours. Two of

these patients died during hospitalization. Two more of these patients died within 2 months.

Ventricular function curves may be characterized not only by the rate of rise of the curve but also by the height to which it rises before it becomes flattened. This latter characterization may be called the asymptote. All but three patients in this study reached stroke indices greater than 20 cc/min per  $m^2$  with volume infusion (Fig. 4). Each of these latter three patients had congestive heart failure and two did not survive hospitalization. In addition each of the three had a ratio  $\Delta$  stroke index/ $\Delta$  filling pressure of less than 0.30 cc/mm Hg. The curves in these patients clearly showed depressed myocardial function by inspection as well as by these two criteria.

The rapid LMWD infusion consistently resulted in an elevation of the filling pressure of the left ventricle. When the filling pressure was initially between 7 and 20 mm Hg, infusion of 200 cc LMWD resulted in a rise of 2–3 mm Hg, and infusion of 400 cc LMWD in a rise of 5–6 mm Hg in filling pressure. Of the 25 volume augmentation studies, in 18 the initial filling pressures were in this range of 7–20 mm Hg and 17 of these had linear infusion–filling pressure changes which paralleled each other. The added volume ( $\Delta V$ ) could be related to the change in filling pressure ( $\Delta P$ ) by the ratio  $\Delta V / \Delta P$  or  $400 / 5-6 = 65-80$  cc/mm Hg as an estimate of diastolic left ventricular compliance. In the same manner when the initial left ventricular filling pressure prior to added LMWD was elevated to 22–29 mm Hg in four curves (R. D. two curves, C. N. and C. G., one had been in overt congestive heart failure within hours and two others had ventricular gallops during the curves) infusion of 200 cc LMWD resulted in an average rise

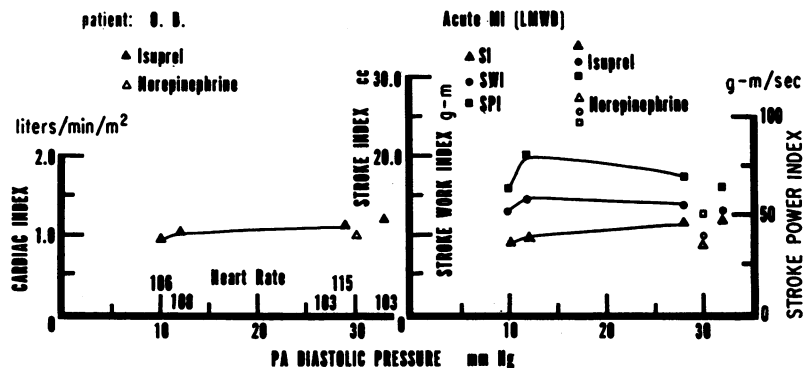


FIGURE 3 Left ventricular function curves in a patient with acute myocardial infarction. Left ventricular function curves relating cardiac index, stroke index, stroke work index, and stroke power index to pulmonary artery end-diastolic pressures. There is little rise in these parameters despite a large rise in filling pressure. It is noteworthy that the base line parameters of function were depressed in this patient, who received 200 ml dextran in 100-ml increments. See legend for Fig. 1.

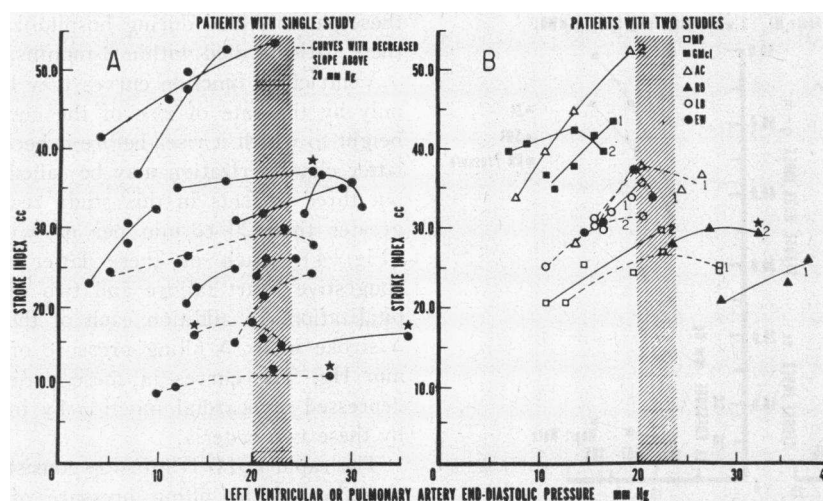


FIGURE 4 A and B. Composite of ventricular function curves relating stroke index to left ventricular end-diastolic pressure or pulmonary artery end-diastolic pressure. In these patients with acute myocardial infarction, an increase in stroke index (and other descriptors of function) generally continued until the left ventricular filling pressure reached 20–24 mm Hg (solid curves) and beyond this pressure the curves tended to flatten or decrease (dashed curves). Similar symbols in 4 B identify both curves in the patients in whom two curves were performed. The first and second curve in each patient are numbered 1 and 2. During the second curve for E. W., the rhythm was irregular. In addition a star identifies each of the five curves whose ratio  $\Delta SI/\Delta F P$  was less than 0.30 cc/mm Hg. See text for further discussion.

of filling pressure of 9 mm Hg. For these patients with initial elevation of filling pressure the estimated diastolic cardiovascular compliance could be calculated as 200/9 or approximately 20–25 cc/mm Hg. This would seem to indicate that when the initial filling pressure was elevated the left ventricle was less compliant.

In the ventricular function curves in these patients with acute myocardial infarction, an increase in ventricular performance (stroke index, etc.) continued until the left ventricular filling pressure reached 20–24 mm Hg. Beyond that critical range of left ventricular filling pressure, the slope of the ventricular function curves tended to flatten or actually decrease in nine curves (Fig. 4).

Following the volume expansion with LMWD, the cardiac index remained elevated in five patients for an average of 6 hr (range 4–10) before declining to the initial level (Fig. 5). During this time the filling pressure fell gradually paralleling the fall in cardiac index. In patient R. D. the cardiac index remained elevated above control values while the filling pressures declined toward the starting level over 13 hr. Thus, this patient maintained a higher cardiac output at a lower left ventricular filling pressure. This observation suggests an increased contractility, an altered myocardial distensibility or a decreased afterload following volume augmentation in this patient. Decreased afterload is a less

likely explanation in this patient as the aortic blood pressure dropped similarly in all patients during the hours following dextran infusion. This persistence of cardiac index elevation in the patients studied occurred in the presence of normal renal function or slight rise in blood urea nitrogen.

In six patients the ventricular response to infusion of LMWD was compared twice within the first 3 days following acute myocardial infarction. These six patients (M. P., R. D., A. C., L. B., E. W., and G. McI.) had

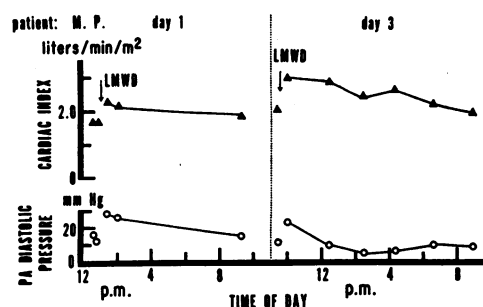


FIGURE 5 Persistence of hemodynamic changes induced by dextran. The cardiac index, once increased by LMWD, gradually returned to its control levels over 4 or more hr. In this patient the fall in left ventricular filling pressure paralleled that of the cardiac output.



an uncomplicated hospital convalescence. In four (M. P., R. D., A. C., and G. McL.) on the 2nd or 3rd day the pulmonary artery end-diastolic pressure before infusion was lower and the cardiac index was higher than during the initial study. In these four, during the repeat study, the cardiac index-filling pressure curve was shifted upwards and leftwards (Fig. 6). The upward and leftward shift of the function curves during the repeat study

indicated improved ventricular performance in each of these uncomplicated patients. In the other two patients (L. B. and E. W.) the cardiac index during the repeat study fell on the same ventricular function curve relating cardiac index to filling pressure, albeit at its lower end (Fig. 7). Both these patients had long standing coronary artery disease with previous myocardial infarctions.

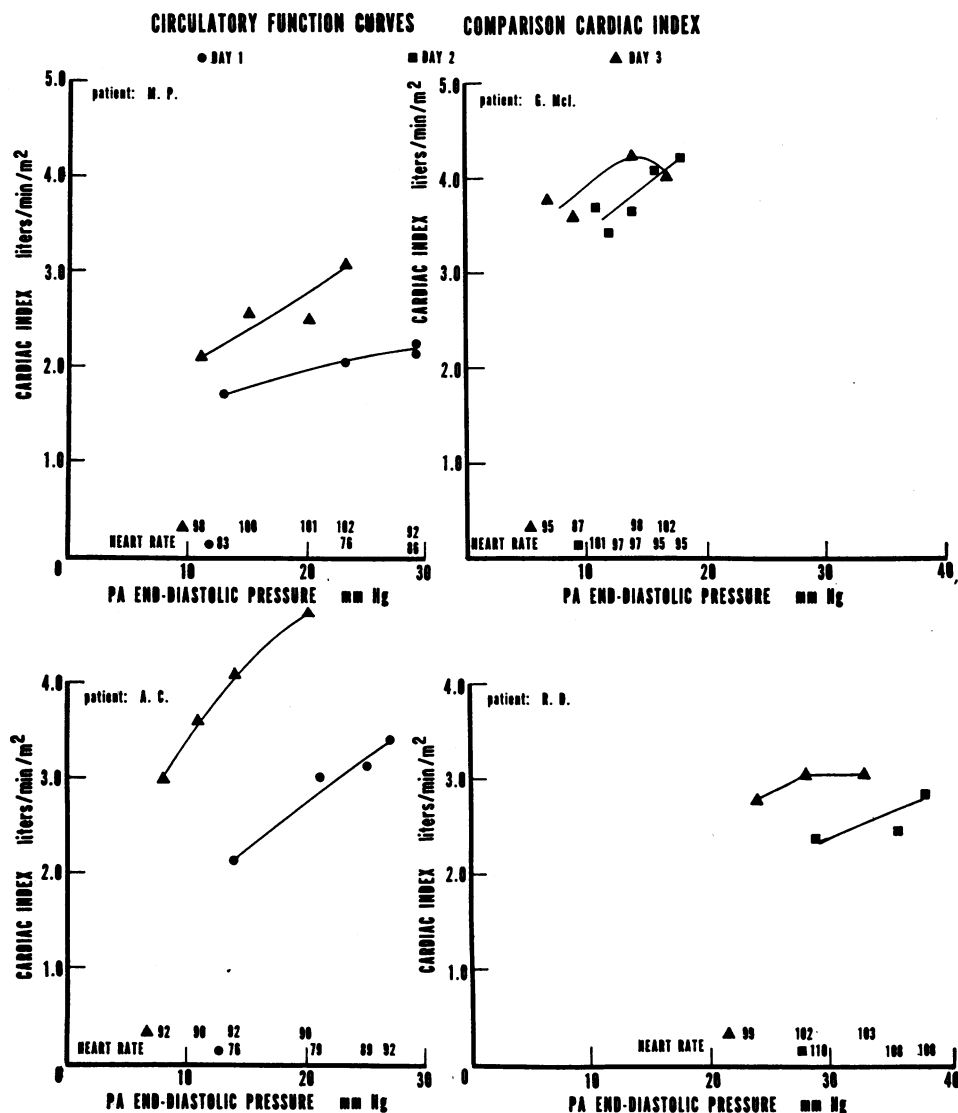


FIGURE 6 Serial ventricular function curves in acute myocardial infarction. Left ventricular cardiac index function curves on day 1 and day 3 in M. P., on day 2 and day 3 in G. McL., on day 1 and day 3 in A. C., and on day 2 and day 3 in R. D., after acute myocardial infarction. On the repeat curve during early convalescence the pulmonary artery end-diastolic pressure prior to infusion was lower and the cardiac index was higher. The ventricular function curves are shifted upwards and to the left on the repeat study, suggesting improved ventricular performance during early convalescence. See legend for Fig. 1 for abbreviations and text for discussion.

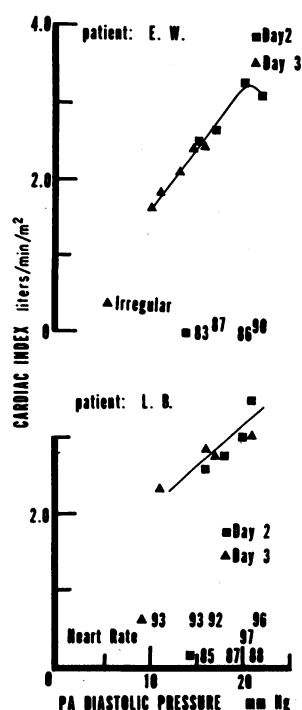


FIGURE 7 Serial ventricular function curves in acute myocardial infarction. Left ventricular function curves on day 2 and day 3 in E. W. and L. B. In these two patients the cardiac index during the repeat study fell on the lower end of the same ventricular function curve. Both patients had long-standing coronary artery disease with previous myocardial infarctions. See text for discussion.

## DISCUSSION

Several aspects of the methodology in the present study require comment. Measurements of low cardiac output are imprecise by many techniques including the dye dilution method. Central injection and sampling sites for the indicator as performed in this study would tend to improve the accuracy of measurement. However, the trend of cardiac output change was more relevant than the precise measurement for the results of this study. Variability in dye dilution cardiac outputs in these non-steady-state acutely ill patients could have influenced the results, but agreement between duplicate base line determination averaged 6.4% ( $SD = \pm 4.4$ ) (17) in these patients. In addition, dye calibration before and after LMWD infusion in the patients has shown no consistent variation in calibration factor. Experimentally, anemia produced by LMWD infusion with a change in oxygen-carrying capacity will increase cardiac output (23–27). It is unlikely that a fall in venous hematocrit averaging 3 vol % would significantly influence these ventricular function curves. Since the body hematocrit (in the capillary bed) is usually 91% of the venous hematocrit (28, 29), it is possible that body hematocrit

was even lower following dextran infusion, though plasma or red cell volume measurements were not made. Also the change in ventricular performance as a function of heart rate alterations (treppe phenomenon) would have no important effect in this study as the heart rate in individual patients varied little at all during infusion. Finally, the pulmonary artery end-diastolic pressure has been shown to be a reliable index of left ventricular end-diastolic pressure assuming a normal mitral valve and normal pulmonary vascular resistance (30). The two pressures were recorded simultaneously on 20 occasions in four patients in this study, in three patients before infusion, and in one during dextran infusion. Pulmonary artery end-diastolic pressure correlated with left ventricular end-diastolic pressure for these points with  $r = 0.95$  (20).

Even the briskly rising ventricular function curves tended to become flattened or decreased above a filling pressure of 20–24 mm Hg. Several mechanisms might be operative. First, the elastic limits of the left ventricle and (or) pericardium might have been reached at 20–24 mm Hg filling pressure. Further volume augmentation would result in filling pressure elevation without further significant myocardial stretch and thus insignificant stroke volume increase. A right atrial pressure which rose approximately equally with left ventricular filling pressure would lend support to this explanation. Right atrial pressure was measured during six curves in four patients. In three curves it did rise equally with left ventricular filling pressure. However, in the other three curves it did not. Thus the data neither support nor deny this conjecture. Second, the function curves may flatten when the ventricle is stretched beyond the elastic limits. Third, acute dilatation of the ventricle with volume augmentation, may result in regurgitation through the atrioventricular valves. No data were accumulated in this study to bear on the latter two speculations. These possibilities are not mutually exclusive, however, and any or all may underlie the observed flattening of the curves.

The presence of a descending limb of the Starling curve in several patients is an important observation from these data (Fig. 4). This is the first time this has been demonstrated in patients with acute myocardial infarction. A descending limb has been produced on left ventricular function curves consequent to restriction of left coronary flow in dogs (31). Above the 20–24 mm Hg filling pressure range in these patients, the stroke index and other parameters are not only not increased, but may actually fall. These data would indicate that there is no advantage to elevation of the filling pressure beyond the 20–24 mm Hg range in such patients to try to increase the cardiac output quite apart from the risk of developing pulmonary edema. In addition, when the initial filling pressure is elevated beyond 20–24 mm

Hg, avoidance of pulmonary edema may be possible by reducing the filling pressure to this range with little or no decrease of cardiac output.

The hemodynamic effects of dextran in shock of diverse etiologies include increased central venous pressure, cardiac output, stroke volume, stroke work, and arterial blood pressure and decreased mean transit time, hematocrit, and blood viscosity (14, 32-35). Normal subjects and patients with shock of various etiologies may undergo an increase in cardiac output without a prerequisite hypovolemia (14). Less information exists as to its hemodynamic effects in acute myocardial infarction (12, 14). Of 12 patients with hypotension or shock due to an acute myocardial infarction studied by Gunnar, Pietras, Stavrakos, Loeb, and Tobin (12) and by Cohn, Luria, Daddario, and Tristani (14), nine exhibited hemodynamic improvement following LMWD judged by right atrial pressure, cardiac output, stroke volume, and stroke work, but three showed a precipitous rise of right atrial pressure. Left ventricular filling pressure was not measured in these patients and it is possible that in some it was elevated initially. Left ventricular end-diastolic pressure in shock after acute myocardial infarction is frequently elevated while central venous pressure is normal (5). Knowledge of left ventricular filling pressure becomes useful in directing the course of therapy when LMWD is being considered in acute myocardial infarction. The efficacy of LMWD, per se, in reducing the mortality in acute myocardial infarction is controversial (36-38). However, increased coronary flow theoretically should occur because of decreased blood viscosity (39) and diminished cellular aggregation (40) as well as the modest elevation of aortic diastolic pressure present after blood volume expansion with LMWD.

In patients with acute myocardial infarction, left ventricular performance can be assessed by relating cardiac output and related parameters to ventricular filling pressure after dextran infusion. The initial left ventricular filling pressure and cardiac output, the rate of rise or slope of the function curve after dextran infusion, and the asymptote or flat portion of the curve all characterize myocardial performance. If the initial left ventricular filling pressure is elevated, the initial relationship between cardiac output and filling pressure may indicate that the ventricle is operating on a different function curve. Also, the elevated filling pressure may reflect the altered ventricular distensibility after the acute myocardial infarction. The rate of rise or slope of the ventricular function curve demonstrates the ventricular response to an increase in preload. The limit of ventricular function or distensibility in response to the dextran infusion is defined by the asymptote. Since the left ventricular function curves during the early con-

valence were shifted upwards and to the left when compared to the initial curve such observations could suggest improved ventricular performance during convalescence even in patients with a relatively uncomplicated illness (Fig. 6). In the two patients with previous myocardial infarctions, the cardiac index response to volume expansion fell on the lower end of probably the same ventricular function curve (Fig. 7). These patients may have had more generalized myocardial disease, or coronary cardiomyopathy. During early convalescence they worked on a lower portion of the ascending limb of their function curve and thus encroached less on their cardiac reserve than initially after the infarction.

In conclusion, a method of evaluating left ventricular performance during the course of an acute myocardial infarction has been demonstrated. By this method of cautiously expanding blood volume, and elevating left ventricular filling pressure, cardiac output and stroke volume, stroke work, and power can be improved. It is possible to maintain this increased cardiac output for at least 4 hr and frequently longer. A flattened ventricular function curve is associated with a high mortality in the succeeding days to weeks.

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