Effects of Beta-Adrenergic Blockade in Acute Myocardial Infarction: Evaluation by Radionuclide Ventriculography

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In acute myocardial infarction, beta-adrenergic blockade might depress left ventricular contractility or improve contractility by reducing ischemia. Gated equilibrium radionuclide ventriculography and cuff blood pressure were employed in 10 patients to assess the left ventricular systolic pressure/volume (P/V) ratio as an index of contractility before and after intravenous metoprolol 9.3 ± 2.5 hr after onset of infarction. In 13 normal subjects, the baseline left ventricular PV ratio was 3.5 and the left ventricular ejection fraction (LVEF) was 70%, both greater than the patients with infarction. In the patients after blockade, the systolic blood pressure decreased ($p = 0.02$), and the left ventricular end-systolic volume increased ($p = 0.003$), thus decreasing the P/V ratio from 1.7 to 1.4 ($p = 0.003$), while the ejection fraction (EF) was unchanged (55% versus 52%). The right ventricular ejection fraction (RVEF) decreased from 50% to 43% ($p = 0.004$). Thus, radionuclide ventriculography demonstrated that left ventricular contractility was reduced in patients with acute myocardial infarction and that beta-adrenergic blockade further decreased left ventricular contractility and right ventricular performance.

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Gated equilibrium radionuclide ventriculography (RVG) is an accurate technique for quantitating left ventricular (LV) function (*1,2*), and this method has been employed in patients with ischemic heart disease to assess the effect of surgery (*3,4*) and drugs (*5*). Because beta-adrenergic blockade (beta-blockade) reduces mortality after acute myocardial infarction (*6–8*), there is interest in its effects during acute infarction. In this setting, beta-blockade can decrease ventricular tachyarrhythmias (*9*), myocardial lactate production and oxygen demand (*10*), infarct size if given early in man (*11,12*) and dogs (*13,14*), and possibly mortality (*15–17*).

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Acute beta-blockade decreases LV contractility in animal models of ischemia (*18–20*), as measured by the rate of rise of LV pressure (dP/dt), but this effect could be beneficial or detrimental. While blockade is apparently well tolerated in patients with acute infarction, there have been few studies of its effects on cardiac contractility. The cardiac output and stroke volume decline after blockade (*21*), but these measurements are only indirect indices of contractility because they depend on heart rate and LV loading conditions. A recent study in patients (*22*) showed that dP/dt decreased moderately after intravenous (i.v.) metoprolol given ~1–2 days after the acute event. Earlier studies would improve the ability to assess risks of precipitating heart failure in patients with acute infarction and to define which groups would be at greatest risk. Thus, we employed RVG and the concept of systolic pressure-volume (P/V) relations to estimate LV contractility (*23–27*) and right ventricular (RV) performance before and after intravenous (i.v.) beta-blockade. Patients were studied at an average of 9 hr after the onset of infarction. The results were compared to a group of normal subjects and to changes in plasma catecholamines.

MATERIALS AND METHODS

Study Population

Twenty-five consecutive patients with acute myocardial infarction were screened and 13 qualified for inclusion in this study. Patients were excluded who had sinus bradycardia (45 beats/min or less), electrocardiographic PR interval prolongation (beyond 0.28 sec), second- or third-degree atrioventricular block, systolic blood pressure below 100 mmHg, moderate-to-severe pulmonary congestion judged by rales above the lung bases, bronchospastic pulmonary disease, or prior treatment with beta-adrenergic blocking drugs. All patients gave informed consent on a form approved by our institutional review board. After study, three patients were excluded, leaving a group of 10. One was excluded because of computer malfunction and one because of data overwrite. A third was excluded because she was eventually found to have no necrosis and normal coronary arteries despite typical prolonged ischemic chest pain and electrocardiographic T-wave changes consistent with acute anteroseptal ischemia.

All 10 patients were male. Their ages ranged 48–62 yr (mean 55 yr), and weights ranged 61–102 kg (mean 83 kg). Eight patients had anterior or lateral infarctions. Two had interior infarctions. Therapy prior to study included i.v. lidocaine (8 patients), i.v. nitroglycerin (10 patients), and streptokinase (10 patients; 8 intravenous, 2 intracoronary). All patients had coronary angiography during or after infarction. Patient 2 had collateral supply to the infarct-related artery, but no others did. Patients 3 and 4 had intracoronary streptokinase, but the infarct-related artery did not re-open. Coronary angioplasty was attempted in Patients 5 and 6 and was successful in the latter. Patient 7 had rapid clinical and electrocardiographic evidence of reperfusion after i.v. streptokinase. No other patients had evidence of reperfusion, although the stenotic infarct-related arteries were patent in all except Patients 3–5 when visualized. The timing of possible reopening was uncertain except in Patients 6 and 7 in whom it was <4 hr after the onset of symptoms of infarction.

Study Protocol: Myocardial Infarction Patients

Patients were studied in our Cardiac Care Unit at an average of 9.3 ± 2.5 hr after the onset of symptoms of infarction. The study was designed to examine LV contractility and was not intended to assess the question of myocardial salvage, for which a larger number of patients treated earlier would be necessary (*28*).

An i.v. cannula was inserted for blood drawing. Blood pressure and heart rate were measured once a minute during radionuclide imaging (see Imaging). Blood for plasma catecholamines was drawn before and 10 min after administering the beta-adrenergic antagonist metoprolol intravenously. The blood pressure was obtained by arm cuff sphygmomanometer in six patients and by femoral artery catheter in four patients. Three 5-mg doses of metoprolol were administered intravenously according to a protocol similar to that used in large-scale clinical trials (*16*). A 1-mg test dose was given as part of the first 5 mg, followed by the next two 5-mg doses over 2–3 min at 5-min intervals, if there was no hypotension or bradycardia. Nine patients received 15 mg metoprolol and one received 10 mg. No other medications were initiated or discontinued during the study period.

Study Protocol: Normal Subjects

Previously 13 subjects were recruited by written announcements at this medical center. Their ages ranged 21–69 yr (mean 33 yr) and weights ranged 51–91 kg (mean 70 kg). All had normal physical examinations, took no medications, and were studied in the postabsorptive state. Blood pressure and radionuclide data were collected similarly to the patients with infarction. There were LV data available for 13 subjects and RV data for 8, because magnification excluded a corner of the RV in 5. Data regarding their LV end-systolic P/V relations were reported in part previously (*29*).

Imaging

For the patients, red blood cells were labeled in vivo (*30*) by injecting 1.5 mg of stannous pyrophosphate (Mallinckrodt, St. Louis, MO) and 750 MBq of ^{99m}Tc as pertechnetate intravenously. Cardiac blood-pool images were obtained using a low-energy, all-purpose collimator attached to a portable scintillation camera (Technicare Series 120, GE Medical Systems, Milwaukee, WI) interfaced to a mobile computer (ADAC Micro 3300, Milpitas, CA) using 30–40 ms/frame, 20 frames/cardiac cycle and a 64 × 64 image matrix. Five-minute images were obtained first in the anterior and then in the left anterior oblique (LAO) projection that optimized separation of the ventricles. Then, without moving the camera or patient, metoprolol was administered. Ten minutes later we collected a second image in the same projection, followed by a second anterior image. For volume estimation, 5-ml blood samples were drawn after each oblique image and transferred to Petri dishes using a pipette with 0.5% accuracy (Oxford, Sherwood Medical, St. Louis, MO), counting them for 5 min on the face of the same camera-collimator system.

For the normal subjects, radionuclide images were collected using a low-energy, all-purpose collimator attached to a PhoGamma IV scintillation camera (Siemens, Hoffman Estates, IL), interfaced to a PDP 11/40 computer (Digital Equipment, Maynard MA). Blood samples were collected and counted as above.

Data Analysis

The blood pressure and heart rate were averaged over the 5-min RVG acquisition time. The RV and LV volume and ejection fraction (EF) were calculated in duplicate using validated, user-developed software for border definition (*2*) and separate regions of interest for end-diastole, and end-systole. With this, in 18 other patients the correlation coefficient for contrast and radionuclide LVEF was 0.93, where radionuclide = 0.02 + 0.93 (contrast) ($p < 0.001$). The LV volume was determined using a volume equation without attenuation correction after the method of Dehmer et al. (*31*). With this, in nine other patients the correlation coefficient for radionuclide and contrast volumes was 0.94 (combining end-diastole and end-systole), where radionuclide = −3.16 + 0.22 (contrast) ($p < 0.001$). A similar technique was used for the RV data. Previous work has shown strong relations between RV volume estimated by radionuclide and contrast ventriculography (*32,33*). A close correlation was found previously between blood pressure estimated by cuff sphygmomanometer and ascending aortic recordings. In nine consecutive catheterized patients, for systolic pressure, cuff = −1.68 + 1.03 (aortic) ($r = 0.991$, $p < 0.001$) (*29*), and in this study the correlation coefficient between systolic pressure by cuff and femoral artery recordings was 0.99, where cuff = −1.9 + 1.02 (artery) ($n = 8$, $p < 0.001$) in four patients before and after metoprolol. The plasma epinephrine and norepinephrine levels were measured by radioimmunoassay (CAT-A-KIT, Amersham, Ontario, Canada).

The ratio of peak-systolic pressure to LV end-ejection volume was calculated as an index of LV contractility. The blood pressure, heart rate, LV P/V ratio, LVEF, RV volume and EF, plasma epinephrine, and norepinephrine were assessed before and after blockade. The relations between the LV P/V ratio and EF were assessed before and after beta-blockade, modifying an approach originally suggested by Sagawa et al. (*27*).

Statistical Analysis

Data were entered into a medical data base management system (CLINFO) supplied to the Vanderbilt Clinical Research Center by the Division of Research Resources, NIH, Bethesda, MD. Analysis of variance, Student's paired and unpaired t-tests, and chi-square analysis were used as appro-

priate. Statistical significance was defined as probability (p) < 0.05.

RESULTS

Tables 1 and 2 list data for the patients and normal subjects. Acute myocardial infarction was documented by the development of electrocardiographic Q-waves and an increase in the serum creatine kinase. Only Patient 4 had a prior infarction. No patient had clinical or electrocardiographic evidence of RV infarction, but Patient 2 had RV apical hypokinesis on RVG, suggesting RV infarction. All patients tolerated the study well. None developed signs or symptoms of pulmonary congestion. Patient 9 received only 10 mg of metoprolol because the heart rate decreased to 48.

Before beta-blockade, the patients' LV function was quite different from the normal subjects, with greater end-diastolic and end-systolic volumes (for both, $p = 0.002$), lower LVEF ($p = 0.001$) and lower P/V ratio ($p = 0.03$). There were no differences between the results of the two patients with known reperfusion and the eight patients without known reperfusion, and thus they were combined into a single group for analysis. After metoprolol, the average heart rate decreased 11 beats/minute, a mean decrease of 16% ($p < 0.001$), and the average systolic blood pressure decreased 9 mmHg (8%) ($p = 0.02$). The mean epinephrine and norepinephrine values exceeded the normal values for supine subjects (*34*). Both concentrations increased slightly after beta-blockade (Fig. 1). The increase in norepinephrine was significant ($p = 0.02$).

After metoprolol, the LV end-diastolic volume increased from 174 to 189 ml, a mean increase of 13% ($p = 0.04$) and the LV end-systolic volume increased from 80 to 92 ml (17%) ($p = 0.003$) (Fig. 2). Figure 3 shows the effects of metoprolol on the LVEF and the P/V ratio. The LVEF ranged from 39% to 67% at baseline. The EF decreased (by any amount) in only 5 of 10 patients, and the decrease in EF was not statistically significant. After metoprolol, the P/V ratio decreased uniformly from a mean value of 1.7 to 1.4, a mean decrease of 20% ($p = 0.003$). A decrease in peak systolic pressure and an increase in end-systolic volume occurred in 8 of the 10 patients.

There was a marked change in RV performance after metoprolol (Fig. 4), as the end-diastolic volume increased from 183 ml to 211 ml, a mean increase of 15% ($p = 0.01$) and the end-systolic volume increased from 94 ml to 122 ml (33%) ($p < 0.001$, $n = 10$). The RVEF decreased sharply from 50% to 43% (13%) ($p = 0.004$). Before beta-blockade, in contrast to the LV results, there was no difference in the end-diastolic volume, end-systolic volume, or RVEF between the normal subjects and the patients with infarction. After blockade, there were still no differences in end-diastolic volume or end-systolic volume, but the lower EF approached statistical significance ($p = 0.05$).

Figure 5 demonstrates the curvilinear relation between the LVEF and P/V ratio and the method for the calculations. The data of the infarct patients clustered near the vertex of the curve while the data of the normal subjects ranged on the horizontal area. Before blockade, the P/V ratio in the normal subjects ranged from 2.2 to 12.3, and the P/V ratio in the patients ranged from 0.8 to 2.8. Only one patient had a P/V ratio exceeding 2.4. Only one patient had a P/V ratio below 1.0 at baseline, and the corresponding LVEF of 39% was the lowest among the patients. Arrows connect the results of the patients before and after beta-blockade. The changes in the P/V ratio and EF ran parallel to the curve in 6 of the 10 patients. In the other four patients, changes were generally perpendicular to the curve because LVEF increased (three patients) or was unchanged (one patient) even though the P/V ratio declined.

DISCUSSION

By radionuclide ventriculography, these patients had moderately reduced LV function (EF and P/V ratio), and the plasma catecholamines were elevated in the early hours of uncomplicated acute myocardial infarction. After metoprolol, the LV dilated and the systolic blood pressure decreased, thereby further reducing the P/V ratio. Simultaneously, RV volume increased and the RVEF decreased sharply. The plasma norepinephrine level increased. All these changes were consistent with reduced contractility as outlined below.

Pressure/Volume Ratio as an Index of Contractility

The slope of the end-systolic P/V relation (the end-systolic elastance, E_{es}) is an index of contractility (*23–25*), which is relatively independent of end-diastolic loading conditions, influenced only moderately by heart rate (*26,35*), approximately linear in the normal operating range (*36,37*) and described by the equation:

$$E_{es} = P_{es}/[V_{es} - V_o],$$

where P_{es} is the ventricular pressure at end-systole, V_{es} is the end-systolic volume and V_o is the volume at zero pressure (*38*). The term P_{es}/V_{es} is a reasonable approximation of E_{es} if V_o is close to 0 or if V_{es} is much greater than V_o. However, the numerical value of the P/V ratio is not equal to E_{es}, because the term V_o is neglected. The E_{es} and pressure/volume ratio correlate well (*39*), and both change with the contractile state (*5,24,26,29,40,41*).

In this study, substitution of peak systolic pressure for P_{es} allowed convenient measurement of the peak pressure/end-systolic volume ratio. We employed the

TABLE 1
Patient Characteristics and Hemodynamic Data Pre- and Post-Intravenous Metoprolol

Pt.	Age	MI location	HR		SBP		LVEDV (ml)		LVESV (ml)		LVSV (ml)		LVEF (%)		P/V		RVEDV (ml)		RVESV (ml)		RVSV (ml)		RVEF (%)	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	48	Ant	76	69	127	120	190	170	92	112	98	59	52	35	1.4	1.1	160	189	77	118	83	71	52	38
2	52	Inf	98	83	116	119	199	214	76	93	124	121	62	57	1.5	1.3	176	202	71	105	105	97	60	48
3	57	Inf	75	60	141	114	150	183	49	70	100	114	67	62	2.8	1.8	165	190	100	99	65	91	39	48
4	61	Lat	104	72	128	120	165	187	84	108	81	78	49	42	1.5	1.2	142	149	67	89	75	60	53	40
5	62	Ant	104	94	137	116	120	160	73	91	47	69	39	43	1.9	1.2	91	133	42	72	49	61	54	46
6	50	Ant	72	66	124	119	221	215	102	110	120	105	54	49	1.2	1.0	163	138	73	75	90	63	55	46
7	56	Lat	93	86	116	108	134	139	52	54	82	85	61	61	2.2	2.0	117	135	56	68	61	67	52	50
8	49	Ant	63	53	120	117	146	160	64	65	82	94	56	59	1.8	1.7	120	159	57	91	63	68	53	43
9	56	Ant	57	48	110	107	165	203	54	61	110	142	67	70	2.1	1.8	308	339	169	210	139	129	45	38
10	53	Ant	98	82	122	107	254	262	155	155	99	108	39	41	0.8	0.6	247	262	133	157	114	105	46	40
m	54	—	83	72‡	124	115†	174	189*	80	92‡	94	98	55	52	1.7	1.4‡	183	211‡	94	122‡	89	90	50	43‡
s.d.	4.8	—	17	15	10	5	42	37	32	31	23	26	10	11	0.6	0.4	63	65	39	45	27	22	7	5
s.e.	1.5	—	5	5	3	2	13	11	10	10	7	8	3	4	0.2	0.1	20	21	12	14	9	7	2	2

Pt = patient; MI = myocardial infarction; Ant = anterior; Inf = inferior; Lat = lateral; m = mean; s.d. = standard deviation; s.e. = standard error; HR = heart rate; SBP = systolic blood pressure; LVEDV = left ventricular end-diastolic volume; LVESV = left end-systolic volume; LVSV = LV stroke volume; LVEF = LV ejection fraction; P/V = LV peak systolic pressure/ end-systolic volume ratio; RVEDV = right ventricular end-diastolic volume; RVESV = RV end-systolic volume; RVSV = RV stroke volume; RVEF = RV ejection fraction.

* $p = 0.04$.

† $p \leq 0.01$.

‡ $p \leq 0.003$ pre vs. post. Other values were not significantly different by paired t-tests.

TABLE 2
Hemodynamic Data for Normal Subjects

Subject	Age	HR	SBP	LVEDV (ml)	LVESV (ml)	LVSV (ml)	LVEF (%)	LV P/V	RVEDV (ml)	RVESV (ml)	RVSV (ml)	RVEF (%)
1	21	66	111	56	9	47	84	12.3	146	75	71	49
2	26	75	125	123	37	86	70	3.4				
3	25	56	106	96	27	69	73	3.9				
4	38	73	107	74	29	45	61	3.7				
5	23	55	100	153	45	108	71	2.2	241	131	110	46
6	40	70	126	131	38	93	72	3.3	271	130	141	52
7	31	56	106	97	31	66	68	3.4	95	36	59	63
8	69	63	113	122	57	65	53	2.0				
9	36	46	105	116	32	84	72	3.3	190	111	79	42
10	35	56	112	191	67	124	65	1.7	235	113	122	52
11	28	78	114	127	46	81	64	2.5				
12	29	77	116	134	48	86	64	2.4	210	102	108	52
13	22	60	111	127	42	85	67	2.6	198	117	81	41
m	33	64	112	119	39	80	68	3.6	198	102	96	50
s.d.	12	10	8	33	15	22	7	2.7	56	32	28	7
s.e.	3	3	2	10	4	6	2	0.8	20	11	10	2

Abbreviations are the same as in Table 1.

P/V ratio because it allowed an expression of LV contractility without the necessity of altering pressure or volume during acute infarction to demonstrate E_{es}. Both pressure and volume changed in the direction expected for reduced contractility, with a decrease in pressure coupled to an increase in volume in 8 of the 10 patients with infarction. Changes in pressure and volume in the same direction would reflect either changes in loading conditions or in contractility. The opposite trend, an increase in pressure and decrease in volume, would accompany enhanced contractility. The degree of change of the P/V ratio may not be related quantitatively to the change in the fully developed systolic P/V relation, but the meaning of the directional change was clear. Recently, Dell'Italia and Walsh reported that the maximal rate of LV pressure generation, dP/dt, decreased after metoprolol (*22*). The decrease in P/V ratio agrees with this early systolic measurement of contractility.

Implications Regarding Myocardial Ischemia

In this study, heart rate, systolic blood pressure, the LV P/V ratio, and RV performance decreased after beta-blockade. These factors and the reduction of LV pressure generation and wall stress (*22*) affect myocardial oxygen consumption, which decreases after beta-blockade (*10*). Such reduction in oxygen consumption and in contractility, plus redistribution of blood flow to

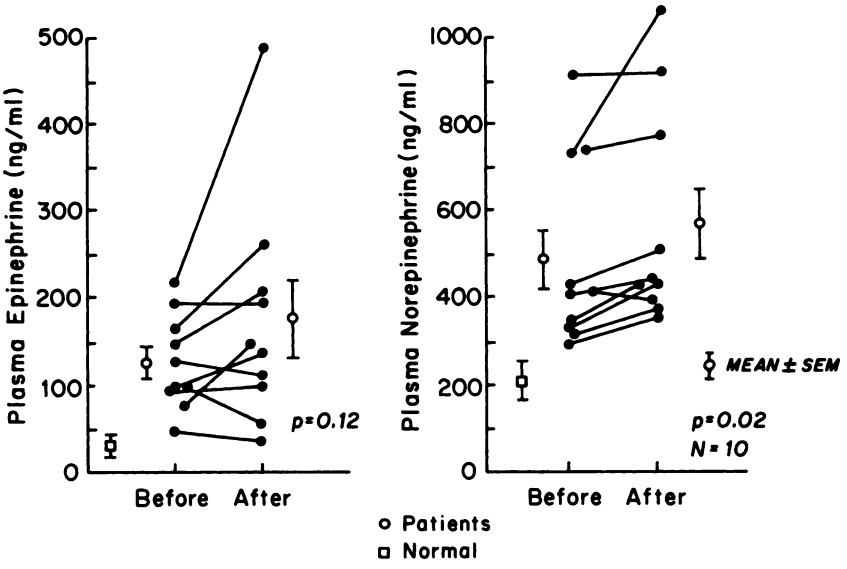

FIGURE 1
Plasma catecholamine levels before and after metoprolol in patients with myocardial infarction. Both epinephrine and norepinephrine exceeded our values for normal supine subjects and were unchanged after beta-adrenergic blockade.

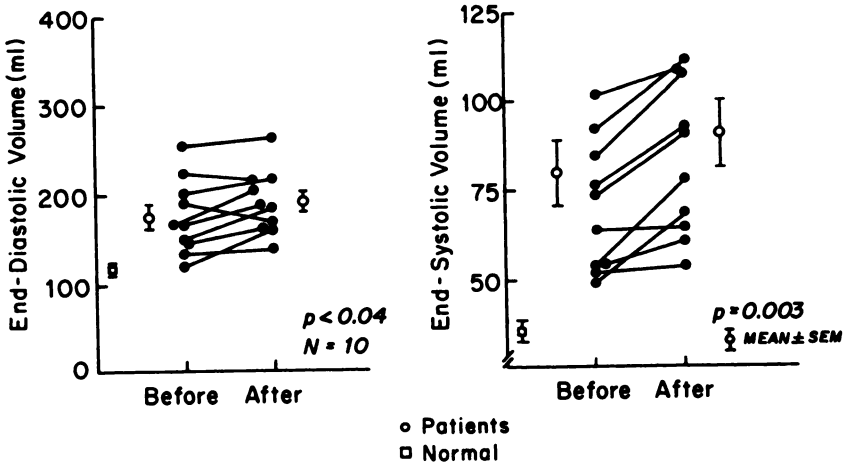

FIGURE 2
Left ventricular volume before and after metoprolol in patients with myocardial infarction. Both the end-diastolic and end-systolic volumes increased. The change was more pronounced for the latter.

the ischemic zone (*19*), might preserve myocardium at risk and might contribute to reduction in infarct size (*11–14*). Breisblatt found that the LVEF improved after metoprolol in patients with collaterals to the ischemic zone (*42*). Similarly, in dogs wall motion improved after beta-blockade (*19,43*) although late infarct size was not reduced by metoprolol (*43*).

The objective of the present study was to assess the effects of acute i.v. beta-blockade on LV contractility in evolving myocardial infarction using the LV P/V ratio. All patients were initially treated with nitrates and streptokinase as part of standard therapy to attempt reperfusion. Because the patients were studied 9.3 ± 2.5 hr after the onset of infarction, myocardial salvage by beta-blockade was not expected. An evaluation of myocardial salvage or mortality reduction would require much earlier treatment (*44*), probably with definite reperfusion (*28,43*) or good collateral blood supply (*42*) and might require large numbers of patients to show the possible effect (*17*). Conversely, we showed a definite, but well-tolerated reduction in contractility in this relatively small group of patients. The timing and rapidity with which the study was performed was likely to preclude a significant effect of time on the results. The predominant effect of metoprolol was probably on the remaining normal myocardium.

The plasma norepinephrine increased after metoprolol as noted by others (*45*). This might have been due to the reduction in cardiac contractility, but other explanations are possible (*45*).

Relation of Pressure/Volume Ratio to Ejection Fraction

The patients' LV function was moderately depressed as judged by both LVEF and P/V ratio. After metoprolol, the P/V ratio decreased uniformly and significantly by 20% ($p = 0.003$) and reflected a decrease in contractility. In contrast, the LVEF did not change consistently or significantly. Thus, LVEF can be maintained by altered loading conditions despite a reduction in contractile state.

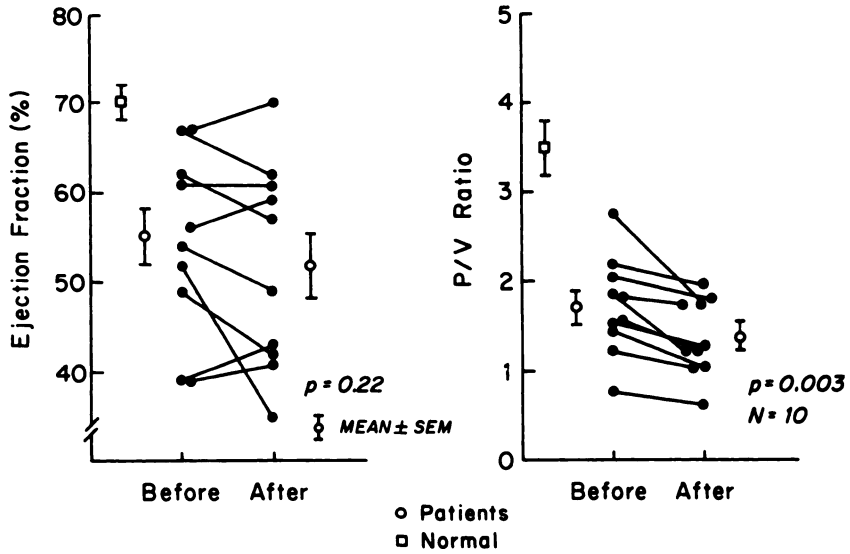

FIGURE 3
LVEF and P/V ratio before and after metoprolol in patients with myocardial infarction. The P/V ratio decreased by 18%, but the change in EF was insignificant.

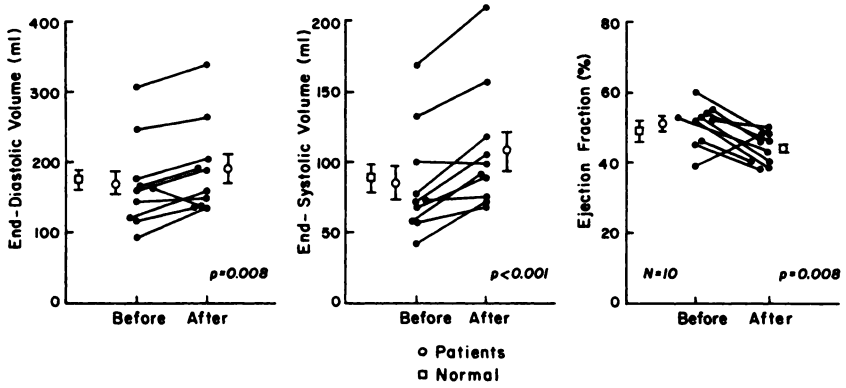

FIGURE 4
Right ventricular volumes and EF before and after metoprolol in patients with myocardial infarction. Volumes increased and EF decreased after beta-adrenergic blockade.

The hyperbolic relation between E_{es} and LVEF was originally derived by using a constant end-systolic volume, end-systolic pressure, and volume at zero pressure while varying end-diastolic volume, and thereby, LVEF (*27*). In this study, despite no control over loading conditions or heart rate, the curvilinear relation between the P/V ratio and LVEF was similar to that described by Sagawa (*27*). Also, changes in the P/V ratio and LVEF after metoprolol generally paralleled the curve (7 of 10 patients), and the range of this family of curves was relatively narrow. These data extend prior studies of the relation between the P/V ratio and LVEF (*26,27,41,46*), which did not assess the effects of beta-blockade. The relation between the P/V ratio and LVEF is such that any further reduction in contractility would be predicted to cause a sharp decrease in LVEF (Fig. 5); this should be avoided in selecting patients for therapy that might decrease contractility. The clinical guidelines for excluding patients with hypotension, bradycardia, and overt clinical congestive heart failure (*16*) caused us to select a patient group with LVEF ≥39%. Patients with more severe infarctions would be expected to have worse LV function and to have a high risk for precipitating overt heart failure with marked reduction in LVEF after beta-blockade.

Effects on Right Ventricular Function

The RV end-systolic volume increased 28 ml (33%) and RVEF decreased from 50% to 43% after beta-blockade in the patients with infarction. These effects probably reflect a decrease in RV contractility. Maughan et al. showed that the end-systolic pressure-volume relation was applicable for describing the RV contractile state in the isolated supported dog heart (*47*). Data for normal subjects are not available, but Konstam et al. showed that RV elastance is less than simultaneous LV elastance in patients with congestive heart failure (*48*). The RV changes in the present study are probably due to a decrease in contractility rather than an increase in afterload, because prior results using metoprolol in a large group of patients with acute myocardial infarction showed no change (*21*) or a decrease (*22*) in pulmonary artery pressure. Thus, with lesser elastance (shallower slope of the P/V relation), small changes in contractility can produce large changes

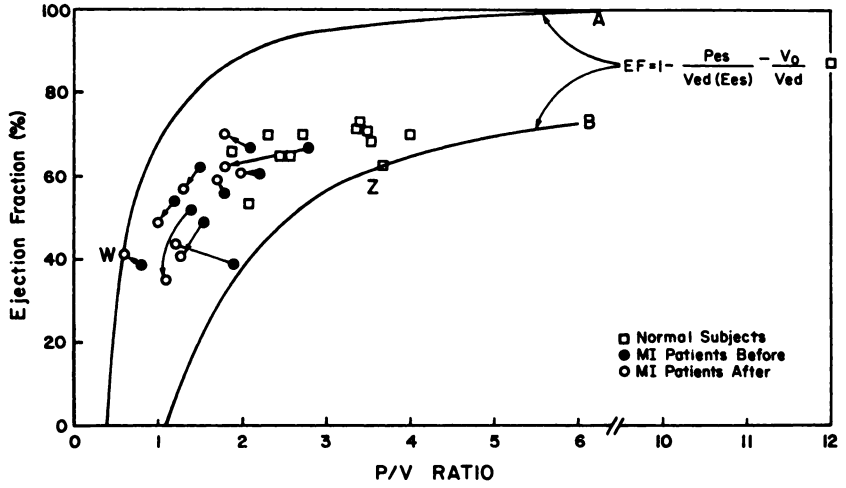

FIGURE 5
Relations of EF and P/V ratio before and after beta-adrenergic blockade. The data of individual patients are connected by arrows. The theoretical relation between E_{es} and EF is shown by the equation of Sagawa et al. (*27*). The outer limits of this family of curves are shown by curves A and B which were generated as follows. The extremes of the actual data were identified (points W and Z). The equation was solved for V_o by substituting the P/V ratio (as a first approximation of E_{es}), peak-systolic pressure (approximating P_{es}), V_{ed} and EF. E_{es} = slope of end-systolic pressure-volume relation; EF = ejection fraction, P_{es} = pressure at end-systole, P/V ratio = ratio of peak-systolic pressure to end-systolic (end-ejection) volume, V_{ed} = volume at end-diastole; V_o = end-systolic volume at zero pressure.

in RV volume. The present study appears to be the first report of RV volume and EF in this setting.

The plasma epinephrine and norepinephrine levels were moderately elevated in our patients. The sharp decrease in RV performance after metoprolol probably reflected blockade of the effects of excess catecholamines on the relatively normal RV. Other mechanisms that might depress RV performance after metoprolol are RV infarction, reduced RV perfusion, or possibly ventricular interaction. Patients with chronic pulmonary disease and RV hypertrophy are prone to develop RV infarction during LV inferior infarction (*49*). None of our patients had pulmonary disease or other reasons to suspect RV hypertrophy with poor RV perfusion. Since only one had any evidence of RV infarction, these mechanisms were unlikely. Lastly, reduced LV pressure after beta-blockade might reduce RV elastance via ventricular interaction (*50*), but the change would probably be small.

Limitations

There were several potential methodologic limitations in this study, which should not affect our conclusions. The possible effects of the timing of beta-blockade and concomitant therapy were discussed above. Our objective was to use RVG to assess ventricular contractility, not to reduce infarct size with beta-blockade.

The radionuclide volume method might have been inaccurate, but prior reports have detailed the accuracy of this technique for assessing LV and RV volume (*2,29,32,33*). Although the possibility of poor RVG reproducibility might have affected the results, the duplicate determination of volume and ejection fraction was designed to decrease such potential methodologic error. In fact, the duplicate results were quite close. There were no significant differences between duplicate determinations of LVEF, end-diastolic volume, end-systolic volume, or the P/V ratio. For example, following metoprolol the mean difference between determinations of end-systolic volume was only 0.3 ml (range 1–6 ml) and the mean difference in the P/V ratio was only 0.02 units (range 0.01–0.19). In a single patient who had two RVG collections after metoprolol, the P/V ratio was 1.34 and 1.27, respectively (0.07 units, a 5% difference). This difference was less than the change after metoprolol in any of the 10 patients.

Correction for intrathoracic attenuation of radioactivity improved estimates of RV volume in one study of adults (*33*), but was less important in another study of children (*32*). Each through variations in attenuation might diminish the overall accuracy of our radionuclide volume estimates, consistent measurements in the same patients should accurately reflect volume changes, and this has been documented in a dog model (*51*). Also, the change in RVEF would be accurate even if absolute RV volume were not. The use of peak or end-systolic pressure affords similar estimates of contractility although results are numerically greater using peak pressure (*24,52*).

The small decrease in heart rate from 83 to 72 beats/minute after metoprolol might have contributed to the reduction in the P/V ratio (*35*). Maughan et al. found an approximate 20% increase in the slope of the end-systolic P/V relation by increasing heart rate from 60 to 80 beats/minute. The decrease in heart rate in our patients was smaller and the P/V ratio decreased by 20%. By linear regression analysis the change in heart rate was not significantly related to the change in the P/V ratio ($r = 0.08$, $p = 0.83$). Thus, the direct effect of metoprolol on the myocardial beta-adrenergic receptors was probably additive to the rate change. The increases in end-diastolic volumes were probably related to the decline in heart rate. This could affect the EF, but not end-systolic indices of contractility (*26,27*).

CONCLUSIONS

By using RVG for estimating LV contractility, it was possible to show more directly than previous studies the role of the beta-adrenergic system in supporting ventricular contractility in acute myocardial infarction. It was demonstrated that LV contractility was significantly depressed in this group of patients with uncomplicated acute myocardial infarction, and the P/V ratio declined further after beta-blockade. This change in contractility was well tolerated in these patients who had no clinical evidence of LV dysfunction. The effect of beta-blockade was quite marked on the RV and was less marked on the LV. This study did not assess whether beta-blockade affected infarct size, but in some patients with coronary collaterals this therapy might preserve ischemic myocardium.

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