Usefulness and Limitations of Vasodilator Therapy in the Treatment of Pump Failure Complicated by Acute Myocardial Infarction

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The factors associated with the development of pump failure in patients with acute myocardial infarction (MI) were studied in 475 patients admitted to our coronary care unit (CCU) and a clinical and hemodynamic re-evaluation of vasodilator and catecholamine therapy was carried out in patients with pump failure. The severity of pump failure as represented by Killip's classification was closely related to left ventricular (LV) dysfunction as judged by LV ejection fraction, number of previous MIs and peak creatinine phosphokinase (CPK) value, and the severity of coronary atherosclerotic lesions as assessed by coronary arteriography. Retrospective hemodynamic analysis of vasodilator therapy (intravenous nitroglycerin, nitroprusside and phentolamine) in 94 patients with pump failure revealed that a significant decrease in pulmonary capillary wedge pressure (PCW) with no significant change in cardiac index (CI) resulted in a clinical improvement in pulmonary congestion in Forrester's hemodynamic subset 2. However, in patients in subsets 3 and 4, the slight increase in CI induced by vasodilator therapy was not enough to restore normal systemic perfusion in spite of a significant decrease in PCW and total systemic resistance; catecholamine was far more effective in increasing CI. Thus, the major indication for vasodilator therapy is in patients of subset 2, while combined use with catecholamine is preferable in those with low cardiac output.

VASODILATOR therapy for the treatment of congestive heart failure was introduced only recently.¹ The basic concepts behind this therapy is that the pump performance of the left ventricle (LV) can be improved by modifying peripheral circulation with vasodilator drugs and that the improvement is not less than that obtained with inotropic agents such as digitalis and catecholamine.^{1,2} The usefulness of this

therapy has been established in patients with pump failure complicated by acute myocardial infarction (MI)^{3,4} and the major focus of interest is now on the clinical efficacy of long-term vasodilator therapy in patients with chronic congestive heart failure.⁵ However, the usefulness and limitations of this therapy still remain to be determined in patients with pump failure of various degrees of clinical and hemodynamic severity associated with acute MI. In this paper presented at the Vasodilator Symposium, we aim through retrospective analysis of the treatment for pump failure, to elucidate clinical and hemodynamic characteristics of pump failure, to re-evaluate vasodilator therapy in the treatment of pump failure, and finally, to discuss the effective-

Key Words:

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TABLE I PATIENTS ENTERED IN THIS STUDY

	Killip's classification				total
	1	2	3	4	
Number of patients	292 (61%)	96 (20%)	37 (8%)	50 (11%)	475 (100%)
Pump failure death	5 (2%)	6 (6%)	7 (19%)	50 (80%)	58 (12%)

	Forrester's hemodynamic Subset				total
	1	2	3	4	
Number of patients	199 (57%)	66 (19%)	43 (13%)	40 (11%)	348 (100%)
Pump failure death	3 (2%)	7 (11%)	6 (14%)	26 (65%)	42 (12%)
Vasodilator therapy	35 (18%)	56 (85%)	16 (37%)	27 (68%)	134 (39%)
(Data available)	35	44	4	11	94
Catecholamine therapy	15 (8%)	26 (39%)	29 (60%)	34 (85%)	101 (29%)

ness and limitations of this therapy compared with catecholamine therapy.

SUBJECTS AND METHODS

Four hundred seventy-five patients admitted to the Coronary Care Unit (CCU) of the National Cardiovascular Center with a diagnosis of acute myocardial infarction (MI) were entered in this study. Of these patients, 386 (81%) and 415 (87%) were admitted within 48 and 72 hours, respectively, from the onset of acute MI. The diagnosis was made when serial electrocardiographic and enzyme changes, as well as a history of typical chest pain, were documented.

The patients were divided into four groups according to Killip's classification⁶ and those in classes 2, 3 and 4 (39% of all patients) were defined as having pump failure (Table I). This classification was used to analyze the clinical and hemodynamic characteristics of patients with pump failure. Swan-Ganz catheterization was carried out for hemodynamic diagnosis on admission in 348 patients. These patients were divided into four groups according to Forrester's hemodynamic subsets⁷ and those in subsets 2, 3 and 4 (43% of catheterized patients) were also defined hemodynamically as having pump failure (Table I). Of those with clinical pump failure (by Killip's classification), 73% belonged to Forrester's subsets defining hemodynamic pump failure; 78% of those with hemodynamic pump failure belonged to the clinical pump failure group. This indicated close agreement between

these two definitions of pump failure.

Of the 348 patients with Swan-Ganz catheterization, 134 and 101 patients received vasodilator and catecholamine therapy, respectively (Table I). The effectiveness of these treatments was assessed from their clinical courses and from the hemodynamic changes in the patients. Of the 134 patients on vasodilator therapy, data on hemodynamic changes were available for 94 patients within 4 hours of beginning vasodilator therapy: 35 in Forrester's subset 1; 44 in subset 2, 4 in subset 3; and 11 in subset 4. In patients in subset 1, the purposes of vasodilator therapy were: reducing high blood pressure for the prevention of cardiac rupture, 21; controlling post-MI angina, 4; trial to limit infarct size, 10. In patients in subsets 2 and 4, the purpose was reduction of pulmonary capillary wedge pressure (PCW). The endpoint of the therapy depended on the patient's condition; however, in most cases, the endpoint was normalization of PCW or a blood pressure level below 100 mmHg. In the latter cases, catecholamine therapy was indicated and hemodynamic data were available for 8 patients on the individual effects of vasodilator and combined catecholamine therapy. In patients in subset 3, guidelines for treatment varied according to the patient's condition and vasodilator therapy was indicated for 16 patients, of whom 4 had hemodynamic data available while catecholamine was indicated for 26 patients, of whom 15 had data available (Table I).

Among the hemodynamic parameters obtained from Swan-Ganz catheterization, PCW and

TABLE II CLINICAL FEATURE OF PUMP FAILURE ACCORDING TO KILLIP'S CLASSIFICATION

	Killip's classification			
	1	2	3	4
Number of patients	292	96	37	50
Age (years)	60.3 ± 10.8	65.1 ± 10.4	63.7 ± 12.4	64.1 ± 11.6
Previous MI (+)	66 (23%)	23 (24%)	20 (54%)**	21 (42%)**
Site of MI				
Anterior	145 (50%)	56 (58%)	26 (70%)	28 (56%)
Inferior	140 (48%)	35 (36%)	10 (27%)	19 (38%)
Others	7 (2%)	5 (5%)	1 (3%)	3 (6%)
Number of patients	191	68	26	22
Peak CPK (IU/L)	1924 ± 1394	2782 ± 1836**	2598 ± 1811*	4094 ± 1852**
Number of patients	152	38	8	3
LV ejection fraction	50.9 ± 10.3	42.4 ± 12.6**	36.3 ± 7.3**	40.0 ± 8.5
Number of patients	169	49	18	33
Coronary lesion				
Normal and SVD	85 (50%)	22 (45%)	5 (28%)	4 (12%)
DVD	49 (29%)	17 (35%)	5 (28%)	14 (42%)
TVD	35 (21%)	10 (20%)	8 (44%)	15 (46%)
	84 (50%)	27 (55%)	13 (72%)	29 (88%)**

* = $p < 0.05$; ** = $p < 0.01$ compared to class 1

(mean ± SD)

Abbreviations: SVD = single vessel disease; DVD = double vessel disease; TVD = triple vessel disease

total systemic resistance (TSR) were used as indices of preload and afterload respectively, and cardiac index (CI) as an index of LV performance.

Of the 391 patients who survived to discharge, 205 underwent cardiac catheterization before their discharge; of the 84 patients who died before discharge, 65 had postmortem coronary angiography at autopsy. These and left ventriculographic findings were used to analyze the clinical characteristics of patients with pump failure.

Statistical Analysis: Values were expressed by mean ± standard deviation (standard error was used only in Fig. 6) and comparisons were made using paired and unpaired *t* tests. A *p* value of less than 0.05 was considered significant.

RESULTS

Clinical and hemodynamic feature of pump failure

Age, incidence of previous MI, site of MI, peak CPK value, LV ejection fraction and coronary arteriographic findings were studied in order to elucidate the clinical feature of pump failure as represented by Killip's classification (Table II). No significant differences were found in age and site of MI among the four groups. The incidence of previous MI was significantly higher in classes 3 and 4 (54% and 42%, respectively) than in class 1 (23%). The peak CPK value obtained from serial CPK curve analysis was significantly higher in classes 2, 3 and 4 than in class 1, especially in class 4, where it was more than double that in class 1. LV ejection fraction obtained from left ventriculography performed before discharge showed a significantly lower value in classes 2 and 3 than in class 1. In class 4, however, the difference was not statistically significant because of small number of cases ($n = 3$). Coronary arteriographic findings including the postmortem study showed differences among the 4 groups. The incidence of multi-

Fig.1. Hemodynamic parameters (mean $\pm$ SD) in clinical subgroups (Killip's classification).

Abbreviations: PCW = pulmonary capillary wedge pressure; TSR = total systemic resistance; LVSWI = left ventricular stroke work index; K = Killip's classification; D = died from pump failure.

Fig.2. Clinical effectiveness of vasodilator and catecholamine therapy. See text for assessment of effectiveness.

Abbreviations: VD = vasodilator; CA = catecholamine; F = Forrester's hemodynamic subset.

vessel disease increased with the severity of Killip's classification, especially in class 4 patients, where it was 88% ($p < 0.01$ compared to class 1). Inhospital mortality increased with the severity of Killip's class and in class 4, it accounted for 84%, among which 80% died from pump

failure (Table I).

Hemodynamic parameters obtained from Swan-Ganz catheterization at admission are shown in Fig. 1, where those who died from pump failure are excluded from the Killip's classification and are grouped in class D (pump

Fig.3. Correlations between changes in pulmonary capillary wedge pressure (PCW) and total systemic resistance (TSR), and changes in cardiac index (CI) with vasodilator therapy.

Fig.4. Hemodynamic changes with vasodilator therapy. Values before and after the treatment are shown by the mean $\pm$ SD and changes are shown by arrows.

Abbreviation: F = Forrester's hemodynamic subset.

failure death). Indices of LV performance, such as CI, stroke index (SI) and stroke work index (LVSWI) decreased in a linear fashion as the Killip's classes advanced and those values were lowest in class D. PCW and TSR as indices of preload and afterload, respectively, increased with the severity of pump failure were highest in class D.

Efficacy of vasodilator and catecholamine therapy

The efficacy of vasodilator and catecholamine therapy in patients with pump failure was assessed clinically and hemodynamically in the 348 patients who underwent hemodynamic monitoring. The therapy was considered effective when patients' physical and laboratory find-

TABLE III HEMODYNAMIC CHANGES WITH VASODILATOR THERAPY

Forrester's subset	HR (b/min)	CI (l/min/m ²)	SI (ml/b/m ²)	PCW (mmHg)	SA (s) (mmHg)	TSR (dynes·sec·cm ⁻⁵)	LVSWI (gm·m/m ²)
Subset 1	C	83.5 ± 12.8	3.31 ± 0.70	40.4 ± 9.0	11.4 ± 4.0	147.3 ± 18.0	80.8 ± 20.5
	VD	84.8 ± 14.8	3.22 ± 0.71	39.4 ± 10.7	8.1 ± 2.3**	119.5 ± 13.9**	63.2 ± 15.7**
Subset 2	C	91.9 ± 22.7	2.88 ± 0.48	33.0 ± 8.6	22.2 ± 3.7	134.1 ± 25.1	60.6 ± 20.3
	VD	92.9 ± 25.1	3.00 ± 0.55	34.8 ± 10.6*	13.8 ± 3.7**	114.3 ± 20.5**	53.4 ± 20.0**
Subset 3	C	76.3 ± 16.7	2.03 ± 0.17	27.8 ± 7.4	14.5 ± 3.9	149.5 ± 16.4	57.5 ± 20.0
	VD	89.9 ± 12.3	2.35 ± 0.60	27.3 ± 9.9	6.5 ± 2.4**	123.8 ± 23.6	45.8 ± 19.4
Subset 4	C	89.6 ± 20.6	1.94 ± 0.18	22.1 ± 4.4	26.0 ± 4.4	122.2 ± 19.7	37.9 ± 8.9
	VD	90.4 ± 16.1	2.36 ± 0.46**	26.1 ± 6.4**	16.8 ± 5.5**	109.5 ± 20.1**	38.3 ± 12.7

* = $p < 0.05$, ** = $p < 0.01$, compared to control value
Abbreviations: C = control; VD = after vasodilator therapy; HR = heart rate; CI = cardiac index; SI = stroke index; PCW = pulmonary capillary wedge pressure; SA (s) = systolic blood pressure; TSR = total systemic resistance; LVSWI = left ventricular stroke work index

(mean ± SD)

ings of left heart failure including chest X-ray, arterial blood gas and urinary output as well as hemodynamic findings improved with therapy (Fig. 2).

Of the patients in Forrester's subset 1, 89% had uneventful clinical courses without any vasodilator or catecholamine treatment, and the mortality was the lowest (2%). In patients in subset 2, the use of vasodilator drugs alone was effective in 50% of patients, while 31% had combined vasodilator and catecholamine therapy, which resulted in improvement in congestive heart failure. The major reasons for the combined use of these drugs were a fall in blood pressure or a lack of improvement in cardiac output with vasodilators. In patients in subset 3, treatment varied according to the patient's condition; catecholamine was effective in 29% of these patients, who increased their cardiac output, with a resultant improvement in their general condition, while vasodilators with or without combined use of catecholamine, were effective in only a limited number of patients (6% and 7%, respectively); a successful clinical course was followed by 28% of subset 3 patients without any of these drugs. In patients in subset 4, the use of vasodilators alone was effective in only 5% of patients, while 25% received combined vasodilator and catecholamine therapy with success. However, in this subset, the number of those with successful results was low and the mortality rate due to pump failure was high (65%).

Hemodynamic assessment of vasodilator therapy

Of the 134 patients under hemodynamic monitoring who received vasodilator therapy, data on hemodynamic changes were available for 94 patients within 4 hours of beginning therapy, during which time no significant changes in clinical condition, such as serious arrhythmias or anginal attacks, were noted. Changes in heart rate (HR), CI, SI, PCW, systolic blood pressure (SAS), TSR and LVSWI with vasodilator therapy are shown in Table III. The drugs used for this purpose were: intravenous nitroglycerin, 57 patients ($0.53 \pm 0.51 \mu\text{g}/\text{min}/\text{kg}$, mean ± SD); nitroprusside, 28 patients ($1.14 \pm 0.82 \mu\text{g}/\text{min}/\text{kg}$); and phentolamine, 9 patients ($2.15 \pm 1.34 \mu\text{g}/\text{min}/\text{kg}$). Statistically significant decreases in PCW and TSR were observed in all subsets, while an increase in CI was seen only in subset 4 and in SI in subset 2 and 4. A significant decrease in LVSWI was seen in subsets 1 and 2. No signifi-

Fig.5. Changes in pulmonary capillary wedge pressure (PCW) and total systemic resistance (TSR) with three vasodilator drugs.

cant changes in HR were noted in any of the subsets.

The relations between changes in CI (Δ CI), and changes in PCW (Δ PCW) and TSR (Δ TSR) are shown in Fig. 3. Changes in PCW and Δ CI correlated poorly ($r = -0.32$, $p < 0.01$) while the correlation between Δ TSR and Δ CI was better ($r = -0.66$, $p < 0.01$), suggesting that afterload reduction may be the principal mechanism for the improvement of cardiac performance.

Means and standard deviations of PCW, TSR and CI before and after vasodilator therapy in each Forrester's subset are given in Fig. 4. The changes in these parameters with therapy are indicated by arrows. As shown on the left, the initial value of PCW was high in subsets 2 and 4 (22.2 ± 3.7 and 26.0 ± 4.4 mmHg, respectively) compared to the values in the other two groups and it decreased to 13.8 ± 3.7 and 16.8 ± 5.5 mmHg (both $p < 0.01$), respectively, after therapy. TSR was high in subsets 3 and 4 compared to the other two groups and the decrease with vasodilators was larger in these two groups (-645 ± 576 and -636 ± 365 dynes $\cdot$ sec $\cdot$ cm $^{-5}$, respectively) than in subset 1 and 2 (-221 ± 321 and -225 ± 314 dynes $\cdot$ sec $\cdot$ cm $^{-5}$, respectively). As shown on the right of Fig. 4, the mean value of CI increased in subset 2, 3 and 4, though only in subset 4 was the result statistically significant. It is noteworthy that, in subset 3 and 4, after

therapy CI is still significantly lower (2.35 ± 0.60 and 2.36 ± 0.46 L/min/m 2 , respectively) than in subsets 1 and 2 (3.22 ± 0.71 and 3.00 ± 0.55 L/min/m 2 , respectively).

In order to clarify the different hemodynamic changes induced by the various vasodilators used, the relationship between Δ TSR and Δ PCW is shown in Fig. 5. The changes produced by nitroglycerin tend to be located on the right side and those produced by phentolamine in the upper left part of the plane. However, when a Δ PCW/ Δ TSR ratio was calculated for each drug, there were no statistical differences among the three drugs.

Role of catecholamine in the treatment of pump failure

Of the patients who received combined vasodilator and catecholamine therapy, data on hemodynamic changes were available for 8 patients who received a vasodilator drug first, followed by combined use of catecholamine therapy. These patients had high PCW (21.3 ± 6.9 mmHg) and low CI (2.26 ± 0.40 L/min/m 2) and belonged to subsets 2 and 4. Hemodynamic data were also available for 15 patients in subset 3, who received catecholamine (dopamine in 12 and dobutamine in 3, 2 to 12 μ g/min/kg) because of low CI (1.86 ± 0.57 L/min/m 2). Hemodynamic changes in these two groups and in

Fig. 6. Hemodynamic changes with vasodilator and catecholamine therapy. Steep lines in the middle and lower groups show changes with the application of catecholamine. Abbreviations: VD = vasodilator; CA = catecholamine.

subset 2 ($n = 17$), in which the patients were successfully treated with vasodilator therapy alone, are given in Fig. 6.

Vasodilator drugs significantly decreased PCW while the increase in CI was minimal as is shown by the upper and middle lines in Fig. 6. In contrast, catecholamine markedly increased CI as is shown by the middle and lower lines of the figure and resulted in a slight decrease in PCW in the middle group.

DISCUSSION

It is generally accepted that vasodilator therapy is indicated in cases with acute MI and high PCW, with or without a decrease in cardiac output.^{3,4} However, there have been no detailed reports on the indications and limitations of vasodilator therapy according to degree of severity or the clinical and hemodynamic subgroups of pump failure. This paper aimed to re-evaluate the position of this therapy in pump failure complicated by acute MI, using a retrospective analysis of the routine management of pump failure in our CCU.

Two classifications, Killip's classes⁶ and Forrester's hemodynamic subsets,⁷ which are

now widely used to indicate the severity of pump failure, were demonstrated to be in close agreement: more than three quarters of patients with clinical pump failure belonged to the hemodynamic pump failure group and vice versa; the deterioration in hemodynamic status was in line with the severity of pump failure as expressed by Killip's classification. Especially, the indices of LV performance (CI, SI and LVSWI) had their lowest values in those who died of pump failure, in spite of maximal compensatory mechanisms (as indicated by highest HR, PCW and TSR).

It is evident from this study that the severity of pump failure is not only related to the extent of LV damage, as indicated by the incidence of previous MI, peak CPK value and LV ejection fraction, but also to the severity of coronary atherosclerotic lesions, as shown by the incidence of multi-vessel disease. These findings are in accord with previous reports,^{8,9} and are considered to be due to alterations in the contractile properties of the heart induced by acute ischemia or infarction,¹⁰ as well as by changes in the LV diastolic pressure-volume relationship, resulting in an elevation of LV end-diastolic pressure and pulmonary edema.¹¹⁻¹³ The high incidence of multi-vessel disease in patients with severe pump

failure suggests the existence of reduced LV compliance associated with infarction and ischemia.⁹

Although vasodilator and catecholamine therapy was given in this study as a part of routine management of pump failure in our CCU and the data were obtained from retrospective analysis, it was clearly demonstrated that the major indication for vasodilator therapy was in those with high PCW and normal cardiac output (Forrester's subset 2). On the other hand, in patients with low cardiac output (subsets 3 and 4), vasodilator therapy alone was shown not to be sufficient to increase cardiac output to normal levels. Catecholamine was far more effective than vasodilator therapy for increasing cardiac output. These findings agree with the previous report by Miller et al,¹⁴ that catecholamine added to vasodilator therapy has major hemodynamic advantages over vasodilator therapy alone in that a greater increase in stroke output can be achieved at much lower LV end-diastolic pressure.¹⁴ However, the use of catecholamine is still controversial in acute MI because it increases myocardial oxygen consumption and induces myocardial ischemia,¹⁵ though, we could find no evidence of any disadvantage in inducing ischemic episodes in the clinical setting, suggesting the usefulness of combined vasodilator and catecholamine therapy in a low cardiac output state.

In our routine vasodilator therapy, intravenous nitroglycerin was used in 61% of patients, while nitroprusside and phentolamine were used in a limited cases to reduce blood pressure. It has been reported that the most important hemodynamic action of nitrates is the lowering of LV filling pressure and thus nitrates are slightly less potent in increasing cardiac output than nitroprusside or phentolamine at equihypotensive doses.¹⁶ This might be one reason why vasodilator therapy caused a small increase in cardiac output in this study. Nevertheless, nitrates have several advantages in the management of pump failure associated with acute MI, compared to other vasodilators: nitrates improve myocardial ischemia by decreasing myocardial oxygen consumption,¹⁷ by enhancing coronary collateral circulation, and by adjusting blood flow to the ischemic area^{18,19} and they produce severe hypotensive side effects less frequently. Nitroglycerin was preferred to other vasodilator drugs for these reasons.

Combined use of vasodilator and catechol-

amine therapy was proven to be effective in the treatment of pump failure. However these treatments still have limitations in severe pump failure such as Killip's class 4 and Forrester's subset 4 as was shown by the high mortality in these groups. This indicates the necessity for further research in the management of pump failure complicated by acute MI.

REFERENCES

1. FRANCIOSA JA, GUIHA NH, LIMAS CT, et al: Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet* 1: 650, 1972
2. COHN JN: Marriage of the heart and the peripheral circulation. Introduction for Vasodilator Symposium. *Prog Cardiovasc Dis* 24: 189, 1981
3. FORRESTER JS, DALUZ PL, WATER DD, et al: The pathophysiology of congestive heart failure. in Cardiac Emergencies (ed. by RS Eliot), Futura Publishing Co. Inc., New York 1977, pp41
4. FORRESTER JS, DIAMOND G, CHATERJEE K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 295: 1404, 1976
5. FRANCIOSA JA: Effectiveness of long-term vasodilator administration in the treatment of chronic left ventricular failure. *Prog Cardiovasc Dis* 24: 319, 1982
6. KILLIP T, KIMBALL JT: Treatment of myocardial infarction in a coronary care unit. *Am J Cardiol* 20: 457, 1967
7. FORRESTER JS, DIAMOND G, CHATERJEE K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 295: 1356, 1976
8. OBERMAN A, JONES WB, RILEY CP, et al: Natural history of coronary artery disease. *Bull NY Acad Med* 48: 1109, 1972
9. MORASKI RE, RUSSEL RO, SMITH M, et al: Left ventricular function in patients with and without myocardial infarction and one, two or three vessel coronary artery disease. *Am J Cardiol* 35: 1, 1975
10. PARKER JO, LEDWICH JR, WEST RO: Reversible cardiac failure during angina pectoris. Hemodynamic effects of atrial pacing in coronary artery disease. *Circulation* 39: 745, 1969
11. DIAMOND G, FORRESTER JS: Effect of coronary artery disease and acute myocardial infarction on left ventricular compliance in man. *Circulation* 45: 11, 1972
12. SWAN HJC, FORRESTER JS, DIAMOND G, et al: Hemodynamic spectrum of myocardial infarction and cardiogenic shock. A conceptual Model. *Circulation* 45: 1097, 1972
13. BARRY WH, BROOKER JZ, ALDERMAN EL, et al: Changes in diastolic stiffness and tone of the left ventricle during angina pectoris. *Circulation* 49: 255, 1974
14. MILLER RR, AWAN NA, JOYE JA, et al: Combined dopamine and nitroprusside therapy in con-

- gestive heart failure. Greater augmentation of cardiac performance by addition of inotropic stimulation to afterload reduction. *Circulation* 55: 881, 1977
15. MAROKO PR, LIBBY P, BRAUNWALD E: Effect of pharmacologic agents on the function of the ischemic heart. *Am J Cardiol* 32: 930, 1973
 16. ARMSTRONG PW, WALKER DC, BURTON JR, et al: Vasodilator therapy in acute myocardial infarction. Comparison of sodium nitroprusside and nitroglycerin. *Circulation* 52: 1118, 1975
 17. HARDARSON T, HENNING H, O'ROURKE RA: Prolonged salutary effects of isosorbide dinitrate and nitroglycerin ointment on regional left ventricular function. *Am J Cardiol* 40: 90, 1977
 18. McANULTY JH, HATTENHAUTER MT, ROESCH J, et al: Improvement in left ventricular wall motion following nitroglycerin. *Circulation* 51: 140, 1975
 19. HORWITZ LD, GORLIN R, TAYLOR WJ, et al: Effects of nitroglycerin on regional myocardial blood flow in coronary artery disease. *J Clin Invest* 50: 1578, 1971