Influence of Vasodilator Therapy on Prognosis of Acute Myocardial Infarction in the Aged Patients

A Comparative Study between Vasodilator-treated Group and Group treated without Vasodilator

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SUMMARY

Influence of vasodilator therapy on prognosis of acute myocardial infarction complicated by left heart failure (in Killip classes II and III) was studied in 22 aged patients (mean age; 75.7 years). The patients were retrospectively divided into 2 groups: Group I; 12 patients were treated with isosorbide dinitrate and/or chlorpromazine and Group II; 10 patients were treated with other conventional medical measures. Initial hemodynamic changes on admission were not significantly different between 2 groups.

With these treatments mortality rate within 2 weeks of treatment was lower in Group I than in Group II ($p < 0.01$), however, cumulative cardiac mortality rate within 18 months did not differ significantly. The present study demonstrated beneficial influence of vasodilator therapy on early prognosis in aged patients, but failed to show prolonged influence on later mortality.

Additional Indexing Words:

Isosorbide dinitrate   Chlorpromazine

IN recent years, growing interest has been focussed on the application of vasodilators to the treatment of acute myocardial infarction (AMI) complicated by pump failure.¹⁾⁻³⁾ Beneficial acute hemodynamic effects of several vasodilating agents have been demonstrated and it has been suggested that vasodilator therapy favourably influences short-term prognosis in patients with severe pump failure in AMI.⁴⁾ However, to the best of our knowledge, there has been no report in which effects of vasodilator therapy on early and late prognosis of AMI was compared to that in control group, not treated with vasodilator. Furthermore, the effect of vasodilator therapy in aged

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Table I. Clinical data and hemodynamic findings

No.	Age	Sex	Infarct location	Previous infarct	Duration between AMI and admission	Killip's classification	Chest X-ray
1	69	M	Inf	Yes	9 days	III	IV
2	68	F	Inf	Yes	<1 day	III	IV
3	77	M	Ant, Lat	No	12 days	III	III
4	79	F	Inf	No	16 days	III	IV
5	77	F	Ant	Yes	<1 day	III	IV
6	71	F	Inf	No	2 days	III	IV
7	78	F	Ant, Lat, Inf	No	2 days	III	IV
8	68	F	Subend	No	<1 day	III	IV
9	71	F	Subend	No	<1 day	III	III
10	80	F	Anterosep	Yes	<1 day	III	IV
11	80	F	Anterosep	No	7 days	II	II
12	74	F	Subend	Yes	2 days	II	II

Abbreviations: Inf; inferior infarction, Ant; anterior infarction, Lat; lateral infarction, Anterosep; anteroseptal infarction, Subend; subendocardial infarction, +; succumbed, ( ); non-cardiac

patients with AMI has not been reported.

This study compares the early and late prognosis in aged patients with AMI treated with vasodilator to that in hemodynamically comparable patients treated without vasodilator.

MATERIALS AND METHODS

Patient population and clinical data:

The study group consisted of 22 aged patients (age ranged from 68 to 83 years, mean; 75.7 years), who were admitted to the coronary care unit of Tokyo Metropolitan Geriatric Hospital during the period between January, 1976 to December, 1977. The patients were selected consecutively from aged patients with AMI in CCU who showed clinical signs of left heart failure (in Killip classes II and III)⁵⁾ and in whom hemodynamic evaluation was made on admission. Patients with no sign of heart failure (in Killip class I) or in shock (in Killip class IV) and patients under age of 60 years were excluded from the study.

Diagnosis of AMI was made on the basis of followings; 1) a history of chest pain or other cardiac symptoms consistent with cardiac ischemia (unless the clinical setting did not permit adequate evaluation of symptoms), 2) diagnostic elevation of serum creatine phosphokinase levels, and 3) serial electrocardiographic changes consistent with the diagnosis.

Clinical data of the patients are summarized in Tables I and II. Severity of left heart failure was assessed clinically on admission and is expressed by Killip's classification.⁵⁾ Roentgenologic findings of left heart failure on admission are classified as follows: class I; normal pulmonary vascular shadows, class II; slight hilar congestion and intensified vascular shadows in the upper lung, class III; class II+

in Group I (vasodilator-treated group)

Cardiac index (L/min/M ²)	Pulmonary artery pressure (mmHg)	Vasodilator		Mortality	
		Drugs	Duration	≤2 weeks	2 weeks~18 months
4.01	60/20	Chlorpromazine	1 day		
2.42	16/9	ISD	90 days		{ + Pump failure
2.37	32/14	ISD	8 days		
2.40	48/22	ISD	18 days		{ + Pump failure
1.85	48/22	ISD	18 days		
2.08	54/30	ISD	12 days		{ + Reinfarction
1.57	34/22	ISD	5 days		
2.45	68/24	Chlorpromazine	1 day		
2.66	45/27	Chlorpromazine, ISD	5 days		{ + Pump failure
1.52	46/22	ISD	4 days		
2.28	24/14	ISD	7 days		{ + (Pneumonia)
2.42	21/10	ISD	11 days		

cause of death.

intensified peripheral vascular shadows, class IV; class III+pleural effusion, marked pulmonary congestion, edema, and cardiomegaly.

Six patients were admitted within 24 hours after the onset of AMI, 4 patients between 24 hours and 48 hours, 2 within 3 days, 5 between 5 days and 1 week, and 4 within 2 weeks.

The patients were divided retrospectively into 2 groups as described below.

Methods:

Hemodynamic study was performed soon after the admission in all cases. Right atrial, pulmonary arterial, and usually pulmonary capillary pressures were monitored with the balloon-tipped floatation (Swan-Ganz) catheter,^{6,7)} arterial pressure was monitored usually through a cannula inserted into the peripheral artery. In a few patients, arterial pressure was measured with a sphyngomanometer. Cardiac output was measured by the thermodilution technique^{6,7)} using the same catheter. Pulmonary arterial end-diastolic pressure was defined as left ventricular filling pressure (LVFP) and following hemodynamic parameters were calculated; stroke volume index (SVI)=SV/body surface area (ml/M²); stroke work index=SVI×(mean arterial pressure–LVFP)×0.0144 (g-m/M²).

Twelve patients (Group I; case 1–case 12, Table I) were treated either with isosorbide dinitrate (ISD) (9 cases) or chlorpromazine (2 cases), or chlorpromazine followed by ISD (1 case). When ISD was administered, usually 5 mg of ISD was administered sublingually every 4 hours or 10 to 15 mg of ISD orally every 6 hours. When chlorpromazine was used, dose of 5 to 10 mg was injected intramuscularly. Drugs and duration of the administration are shown in Table I. Duration of vasodilator therapy listed in Table I indicates the period in which drug administration was rigidly controlled. Digitalis and/or diuretics were used in 5 patients, usually immediately after the admission and prior to hemodynamic study and the institution of vasodilator therapy, and antiarrhythmic agents in 2 patients.

Table II. Clinical data and hemodynamic

No.	Age	Sex	Infarct location	Previous infarct	Duration between AMI and admission	Killip's classification	Chest X-ray
13	67	F	Inf	Yes	3 days	III	III
14	87	M	Subend	No	<1 day	III	III
15	76	M	Inf, Lat	Yes	2 weeks	III	III
16	80	F	Ant	No	5 days	III	IV
17	75	F	Anterosep	No	<1 day	III	IV
18	83	F	Lat	No	5 days	III	III
19	78	F	Subend	Yes	5 days	III	II
20	77	F	Anterolat	No	7 days	II	II
21	74	M	Inf	No	3 days	II	II
22	76	F	Subend	No	2 days	II	II

Abbreviations, as in Table I.

Ten patients (Group II; case 13–case 22, Table II), who did not receive vasodilator therapy, served as the control group. Reasons for not applying vasodilator in these patients included followings; lower arterial blood pressure on admission in 3 patients, associated disorders which prevented the administration of ISD tablets sublingually or orally in 5 patients, and relatively mild symptoms and signs of pulmonary congestion on admission which did not prompt the use of vasodilator therapy in 2 patients. Instead these patients were treated with conventional medical therapeutic measures, including digitalis, diuretics and/or antiarrhythmic agents, when indicated.

The patients were closely followed during post-coronary care and after discharge, but without any definite protocol of treatment. Mortality rate in these 2 groups were calculated as follows; 1) early mortality rate, as defined as mortality rate within 2 weeks of treatment after the admission, and 2) late mortality rate, as defined as mortality beyond 2 weeks after the admission up to 18 months after the onset of AMI. Cumulative mortality rate was calculated as a sum of early and late mortality rate. Causes of death were identified from the hospital records and autopsy findings, and mortality due to cardiac origin was separately evaluated from non-cardiac mortality.

RESULTS

Clinical background and hemodynamic changes in 2 groups:

Age ranged from 68 to 80 years (74.3 ± 1.4 years, mean $\pm$ SE) in Group I and from 67 to 83 years (77.3 ± 1.7 years) in Group II, and they were not significantly different (NS). Previous infarction was present in 5 patients (41.6%) of Group I and 3 patients (30%) of Group II (NS). Location of AMI did not differ significantly between 2 groups; anteroseptal or anterior

findings in Group II (control group)

Cardiac index (L/min/M ²)	Pulmonary artery pressure (mmHg)	Reasons for not using dilator	Mortality	
			≤ 2 weeks	2 weeks~18 months
2.14	68/32	Nausea	+	+
1.82	53/27	Lower BP	Pump failure	
1.81	39/21	Dysphagia due to CVD	+	
1.49	50/22	Nausea	Electromechanical dissociation	
2.40	48/25	Lower BP	+	+
2.30	28/12	Pneumonia	Pump failure	
2.16	26/10	Pneumonia	+	
3.01	29/10	Mild symptoms	Pump failure	
2.94	34/12	Lower BP	+	(Pneumonia)
1.80	28/11	Mild symptoms	Ventricular fibrill.	

Table III. Comparison of hemodynamic changes between Group I and Group II

No. of patients	Group I	Group II	
	12	10	
Age (yrs.)	74.3±1.4	77.3±1.7	NS
Heart rate (bpm)	97.3±4.6	90.5±6.3	NS
Cardiac index (L/min/M ²)	2.33±0.19	2.18±0.15	NS
LVFP (mmHg)	19.5±1.8	18.2±2.5	NS
Systolic arterial pressure (mmHg)	135.0±8.5	119.6±4.2	NS
Mean arterial pressure (mmHg)	100.1±5.0	90.8±4.1	NS
Stroke work index (g·m/M ² /beat)	28.1±3.1	25.6±3.0	NS

infarction was observed in 6 patients (50%) in Group I, while in 3 patients (30%) in Group II, posterior infarction was noted in 3 patients (25%) in Group I and in 2 patients (20%) in Group II. Mean duration between the onset of AMI and the admission to the CCU was 4.5 days in Group I and 5.4 days in Group II (NS).

Hemodynamic changes on admission in 2 groups are summarized and compared in Table III. Heart rate in Groups I and II were 97.3±4.3 and 90.5±6.3 bpm (NS), respectively. Cardiac index tended to be slightly higher in Group I (2.33±0.19 L/min/M²) than in Group II (2.18±0.15), but this difference was not statistically significant. LVFP did not differ significantly between Group I (19.5±1.8 mmHg) and Group II (18.2±2.5 mmHg). Systolic arterial and mean arterial pressure tended to be slightly higher in

Table IV. Comparison of mortality rate between Group I and Group II

	Mortality within 2 weeks		Cumulative mortality within 18 months	
	Group I	Group II	Group I	Group II
Number of patients	12	10	12	10
Killip class II	0/2	1/3	1/2	1/3
Killip class III	0/10	4/7	4/10	6/7
Total mortality	0/12 (0%)	5/10 (50%)	5/12 (41.7%)	7/10 (70%)
Total cardiac mortality	0/12 (0%)	5/10 (50%)	4/12 (33.3%)	5/10 (50%)
	p<0.01		NS	

Group I (135.5 ± 8.5 and 100.1 ± 5.0 mmHg, respectively) than in Group II (119.6 ± 4.2 and 90.8 ± 4.1 mmHg), but differences were not statistically significant.

These results indicate that these 2 groups can be regarded to be comparable in terms of clinical background and hemodynamic changes. These findings support the validity of the assumption that Group II served as the control group for Group I.

Comparison of mortality rate:

Mortality and cause of death are indicated in Tables I and II, and early and cumulative mortality rate in 2 groups are compared in Table IV.

Five patients died within 2 weeks of the treatment with mortality rate of 50% in Group II, while all patients in Group I survived this period. Causes of death in Group II were pump failure in 3, sudden development of electro-mechanical dissociation in 1 and ventricular fibrillation immediately after the discharge from CCU in 1.

Relation between hemodynamic changes and early mortality is illustrated in Fig. 1. While all of 8 patients in Group I in whom LVFP exceeded 18 mmHg (in Forrester subsets II and IV)⁸⁾ survived 2 weeks after admission, 4 patients out of 5 in Group II with comparable elevation of LVFP died in this period.

During the period from 2 weeks after the admission to 18 months 5 patients in Group I died, 3 of them died from pump failure, 1 from recurrent attack of AMI and 1 from pneumonia, while in Group II 2 patients died from pneumonia, but no further cardiac death was noted in Group II during this follow-up period. Therefore, cumulative cardiac mortality rate within 18 months was 33.3% (4 deaths in 12 patients) in Group I and 50% (5 deaths

Fig. 1. Hemodynamic spectrum and prognosis in Group I and Group II. (details, see text)

in 10 patients) in Group II. This difference was not statistically significant. Relation between hemodynamic changes and late cardiac mortality is also illustrated in Fig. 1. Three out of 4 patients who died from pump failure or reinfarction showed elevated LVFP and decreased cardiac index (in Forrester subset IV).

DISCUSSION

It has been shown that vasodilating agents can improve cardiac performance in patients with AMI complicated by pump failure. Hemodynamic improvement has been documented by the administration of sodium nitroprusside,^{9),10)} phentolamine,^{11),12)} nitrates,^{10),13)–17)} and chlorpromazine.^{18),19)} These favourable effects of vasodilator are primarily related to either or both of the decrease in arteriolar resistance (afterload reduction) and the increase in venous capacitance resulting in the decrease in venous return to the heart (preload reduction).

Effects of vasodilators on myocardial metabolism and on regional myocardial blood flow have been extensively studied^{20)–27)} and conflicting results have been reported. It has been also suggested that vasodilators may be potentially deleterious.^{14),24),28)} Relief of pulmonary congestion by nitrates is sometimes accompanied by a significant fall in cardiac output and systemic

blood pressure.^{14),28)} An increase in ST-segment elevation with a decrease in myocardial blood flow in ischemic myocardium in experimental animals has been reported following sodium nitroprusside.²⁴⁾ Influence of these adverse effects of vasodilators on early and late prognosis of patients with AMI has not been fully elucidated.

As to the influence of vasodilator therapy on prognosis of AMI complicated by pump failure, Chatterjee et al⁴⁾ reported vasodilator therapy could improve immediate prognosis in these patients, but the late prognosis remained unfavourable. However, the efficacy of any drug therapy ideally should be evaluated clinically from the results of prospective randomized, controlled trials, although it can not be easily accomplished, if not impossible, in patients with AMI. From this point of view, it can be stated that the effects of vasodilator therapy on prognosis of AMI complicated by pump failure have been inconclusive.

In the present study, although it is a retrospective study, not a prospective randomized study, the influence of vasodilator therapy on early and late prognosis can be compared to the mortality rate in a group of patients with clinically and hemodynamically comparable background who were treated with other therapeutic measures. Although this study is limited to aged patients, and to a relatively small number of patients with clinical signs of heart failure (in Killip class II and class III), effects of vasodilator therapy on early prognosis is clearly demonstrated by the results of no immediate mortality in Group I compared to 50% mortality in Group II. In the present study, patients with AMI in Killip class I and IV were excluded, because in the former vasodilator therapy is not indicated and in the latter vasodilator therapy alone, especially with ISD, has been shown to be less efficacious.^{3),28)}

Treatment of left heart failure in 10 patients of Group II with conventional, medical therapeutic measures including oxygen inhalation, diuretics, and digitalis, but with no vasodilating agent may not involve ethical problems and these approaches in these patients during the period when the present study was performed may be validated from following reasons; 1) favourable influence of vasodilator therapy on prognosis of AMI complicated by pump failure has not been definitely confirmed and 2) these patients individually had a basis against the use of vasodilator, especially of ISD, as listed in Table II. Some cases may demand further comments; in cases 6 and 7 ISD was not used, because difficulty in evaluation of improvement of mild symptoms of left heart failure was anticipated by the association of pneumonia with AMI, and ISD or chlorpromazine was not administered to patients with relatively lower systolic arterial pressure, as cases 2, 5, and 9.

Although the extent of influences of these associated factors in Group II

on early prognosis could not be evaluated, 4 patients in Group II died from severe pump failure, probably suggesting the ineffectiveness of conventional medical measures in this situation. In this regard, possible influence of slightly lower arterial pressure and cardiac indices in Group II, although not statistically significant, on the result of more unfavourable early prognosis can not be denied.

The present study failed to show a definitely favourable prognosis in Group II, when patients who survived 2 weeks after the admission were followed up to 18 months. Cumulative cardiac mortality rate in Group I (33.3%) did not differ significantly from that in Group II (50%). This result may be in accordance with previous report on late mortality by Chatterjee et al.⁴⁾ Although any definite conclusion may be premature from the results obtained in relatively small number of aged patients in the present study, it appears likely that refractory heart failure in these patients as the consequence of extensive myocardial necrosis can ensue, in spite of temporary relief of pulmonary congestion by vasodilating agents in acute stage of AMI. This may imply that vasodilating agents do not substantially reduce the extent of infarcted myocardium, and more rigidly controlled regimen of vasodilators for more extended period of time after AMI may improve the late prognosis in light of the effects of vasodilator therapy in chronic heart failure,^{29),30)} although it remains speculative in patients with AMI.

Aged patients more frequently develop atypical symptoms at the onset of AMI than younger patients.^{31),32)} This sometimes makes early clinical recognition of AMI difficult, and causes a delay in the admission and institution of the definitive therapy for left heart failure as seen in some cases of the present study. It has been also documented that severe complications are more common and mortality rate is higher in aged patients with AMI.^{31),32)} In this regard, the results of favourable influence of vasodilator therapy on early prognosis of aged patients with AMI and left heart failure may be promising and may support the wide use of vasodilators, if indicated. But further efforts to improve the late mortality of AMI is mandatory.

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