Effects of Vasodilator Therapy for Severe Pump Failure in Acute Myocardial Infarction on Short-term and Late Prognosis

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SUMMARY Forty-three patients with severe pump failure complicating acute myocardial infarction were treated with vasodilators (nitroprusside (40) and phentolamine (3)) for four hours to 27 days. Cardiac index, stroke volume index, and stroke work index (SWI) increased while the left ventricular filling pressure (LVFP) decreased during vasodilator therapy. Twenty-four of the 43 patients (56%) survived. Of patients with initial SWI between 11-20 gm-m/m² and LVFP < 15 mm Hg, 68% survived. In contrast only 18% of patients with SWI of 10 gm-m/m² or less and LVFP > 15 mm Hg survived. Of the 17 patients with clinical shock, 8 (47%) survived.

BENEFICIAL HEMODYNAMIC EFFECTS of vasodilators in patients with myocardial infarction complicated by pump failure have been demonstrated.1-4 It has also been suggested, in a relatively small number of patients, that vasodilator therapy may reduce the hospital mortality even in the presence of severe pump failure.5 However, larger experience is needed. Furthermore, the long-term prognosis of these patients initially treated with vasodilators is not known. This study reports the immediate and late prognosis in 43 patients with myocardial infarction and severe pump failure treated with vasodilators. Results indicate that improvement in the immediate prognosis in these patients might occur with vasodilator therapy. However, the late prognosis remains unfavorable.

Patient Population and Clinical Data (table 1)

Forty-three patients (10 females, 33 males, ages 46 to 74 years) with historical, ECG, and laboratory evidence of myocardial infarction treated with vasodilators in the Myocardial Infarction Research and Intensive Cardiac Care Units of Cedars of Lebanon Hospital, Los Angeles, form the patient population. Twenty-six patients had anterior, ten inferior, three both anterior and inferior, one posterior and one subendocardial infarction. In two patients, the location of infarct could not be determined due to the presence of left bundle branch block. Thirty of the 43 patients had historical and ECG evidence of old myocardial infarct. Thirty-one patients had cardiomegaly on chest X-ray, 17 had clinical shock, and all patients had pulmonary edema. Shock was diagnosed when the clinical features of diminished organ perfusion (cold, clammy skin, mental obtundation and oliguria) and hypotension (systolic blood pressure by cuff, 90 mm Hg or less) were present.

Hemodynamic Monitoring during Intravenous Vasodilator Therapy

Arterial pressure (AP) was monitored usually through a 20 gauge cannula inserted into the radial artery. In a few patients, AP was monitored by inserting a cannula either in the brachial or the femoral artery. Right arterial (RA), pulmonary arterial (PA), and pulmonary capillary wedge pressures (PCW) were monitored with the balloon-tipped triple-lumen flotation (Swan-Ganz) catheter.16 Cardiac output was measured by the thermodilution technique using the same catheter.16,17 To determine the severity of depression of cardiac function and to evaluate the results of therapy, the following hemodynamic parameters were calculated; stroke volume index (SVI) = SV/body surface area (BSA) (ml/m²); Stroke work index (SWI) = SWI × (AP−PCW) × 0.0144 (gm-m/m²), systemic vascular resistance (SVR) = (AP−RA)/C.O. × 80 (dynes sec cm⁻⁴) and pulmonary vascular resistance (PVR) = PA−PCW/C.O. × 80 (dynes sec cm⁻⁴).

Hemodynamic Definition of Severe Pump Failure

Severe pump failure was defined when initial level of SWI was 20 gm-m/m² or less and left ventricular filling pressure (LVFP) was > 15 mm Hg.10 Justification of such classification is based on our previous experience that the immediate prognosis in this group of patients with conventional therapy is extremely poor and the hospital mortality approaches 80%.11

Intravenous Vasodilator Therapy

Initially all patients were treated with intravenous infusion of nitroprusside or phentolamine. Sodium nitroprusside was used in 40 patients and phentolamine in the
remaining three patients. Nitroprusside was infused with the use of an infusion flow controller.* Phenolamine was infused by a constant infusion pump (Harvard). Arterial pressure and LVFP were constantly monitored during initial period of vasodilator therapy. Both drugs were started at a very low dose (nitroprusside — 16 μg/min; and phenolamine 0.1 mg/min). Cardiac indices (C.I.) (cardiac output/body surface area) were determined in duplicate approximately every 15–30 min to evaluate changes in systemic vascular resistance. The standard deviation about the mean of duplicate cardiac output determinations in this study was 5.3%. The dose of nitroprusside or phenolamine was gradually increased until significant beneficial hemodynamic effects were observed (increase in C.I. and SVI with decrease in LVFP). Mean arterial pressure did not decrease more than 20 mm Hg except in one patient in whom it decreased by 33 mm Hg. The infusion rates were then kept constant to maintain the hemodynamic response. In some patients, the infusion rates of the vasodilators needed to be increased to maintain the improved hemodynamic and clinical response. The dose of nitroprusside used varied from 25 to 425 μg/min.

Intravenous vasodilator therapy was continued for four hours to 27 days with monitoring of LVFP, AP, and C.I. In those patients who survived, the dose of intravenous vasodilators was gradually reduced when hemodynamic and clinical improvements appeared to have stabilized. Hemodynamic response of intravenous nitroprusside is usually reversible within 5–10 min following discontinuation of the therapy. Therefore, as the intravenous medication was being tapered off, sublingual isosorbide dinitrate (2.5–20 mg) was administered every 90 min in 30 of the 43 patients to maintain the hemodynamic response to intravenous vasodilator therapy. Sublingual isosorbide dinitrate improves left ven-

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*IVAC 200, IVAC Corporation, San Diego, California
tricular performance in patients with pump failure and the hemodynamic response usually lasts for 90 min.\textsuperscript{13}

Additional Pharmacological Therapy

Forty of the 43 patients received intermittent diuretic therapy (furosemide or ethacrynic acid) along with vasodilator therapy. Twenty patients also received digitalis principally for supraventricular tachyarrhythmias. None of the patients in this study were treated with mechanical circulatory assist devices. Only one of the 43 patients received vasopressor norepinephrine concurrently with nitroprusside for approximately 12 hours.

Short-term Results

Hemodynamic Response during Intravenous Vasodilator Therapy (fig. 1 and table 2)

Before institution of vasodilator therapy, average C.I. was 1.7 ± 0.05 (sem) L/min/m\textsuperscript{2}, with a range of 0.92 to 2.3 L/min/m\textsuperscript{2}. In 42 patients C.I. increased. In the remaining patient, although C.I. remained unchanged, SVI increased during vasodilator therapy. The C.I. increased to an average of 2.2 ± 0.06 L/min/m\textsuperscript{2} (range 1.3 to 3.0). RA, FA, AP, TSVR and PVR decreased with no significant change in heart rate in majority of the patients. Improved left ventricular performance was indicated by increase in SVI (+31.7%) with a decrease in LVFP (-35%). Despite fall in arterial pressure, the stroke work index tended to increase (35.7%).

Complications (table 1)

No major complications were encountered during vasodilator therapy. Three patients developed sudden severe but transient hypotension associated with deterioration of the clinical status. Hypotension was reverted in less than five

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 & Control & Vasodilators & \textit{P} \\
HR (beats/min) & 100 ± 2.4 & 99 ± 2.7 & NS \\
AP (mm Hg) & 83 ± 1.5 & 73 ± 1.7 & .0005 \\
PA (mm Hg) & 39 ± 1.2 & 28 ± 1.1 & .0005 \\
RA (mm Hg) & 13 ± 0.79 & 9 ± 0.61 & .0005 \\
LVFP (mm Hg) & 31 ± 0.98 & 20 ± 0.77 & .0005 \\
C.I. (L/min/m\textsuperscript{2}) & 1.7 ± 0.05 & 2.2 ± 0.06 & .0005 \\
SVI (ml/m\textsuperscript{2}) & 17.3 ± 0.2 & 22.8 ± 0.8 & .0005 \\
SWI (g--m/m\textsuperscript{3}) & 14 ± 0.88 & 19 ± 0.91 & .0005 \\
SVR (dynes-sec-cm\textsuperscript{-5}) & 293 ± 112 & 1435 ± 65 & .0005 \\
PVR (dynes-sec-cm\textsuperscript{-5}) & 275 ± 21 & 188 ± 18 & .0005 \\
\hline
\end{tabular}
\caption{Hemodynamic Changes during Intravenous Vasodilator Therapy}
\end{table}

All values are mean ± standard error of the mean.
Abbreviations: HR = heart rate; AP = mean arterial pressure; FA = mean pulmonary artery pressure; RA = mean right atrial pressure; LVFP = left ventricular filling pressure; C.I. = cardiac index; SVI = stroke volume index; SWI = stroke work index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.
minutes by temporary discontinuation of the drug and elevation of the legs in less than five minutes. Nine patients had hiccough, four nausea, and in three patients mental confusion was observed. Convulsions or involuntary muscular twitching was not encountered in any patient. Blood thiocyanate levels were not routinely monitored; however, in two patients who received relatively larger doses of nitroprusside for a prolonged period the blood thiocyanate level was less than 3 mg/100 ml (toxic level 12 mg/100 ml). Frank hypothyroidism, a known complication of prolonged nitroprusside therapy, was not clinically apparent in any of these patients.

Hospital Mortality

Nineteen of the 43 patients died in the hospital. Fifteen patients died of pump failure despite initial improvement in hemodynamics during vasodilator therapy. Two patients died on the second and third postoperative days (14 and 25 days after hospitalization) following mitral valve replacement. One patient died of ventricular fibrillation on the eleventh hospital day during induction of general anesthesia for axillary artery embolectomy. One other patient reinfarcted and died suddenly on the seventeenth hospital day.

Of 17 patients who presented with clinical shock, nine (53%) died and eight (47%) were discharged from the hospital.

Hospital Mortality and Initial Level of Stroke Work Index (fig. 2)

Of 32 patients with SWI between 11-20 g-m/m², 22 (68%) survived. In contrast, only two (18%) of the 11 patients with SWI of 10 g-m/m² or less survived.

Late Follow-up Results

As sublingual isosorbide dinitrate improves left ventricular performance by increasing cardiac output and decreasing left ventricular filling pressure, and does not increase myocardial oxygen demand, sublingual isosorbide dinitrate therapy was suggested as an additional antifailure therapy to the patients who survived initial hospitalization. However, only 17 of the 24 patients discharged from the hospital continued sublingual isosorbide dinitrate, initially every 90 minutes and later every 4-6 hours. Although a majority of these patients was seen during follow-up by one of us (K.C.) at random intervals, the data reported were obtained from the personal physician by telephone or postcard survey. Only patients treated before June 1974 are included and the survival at June 1975 is presented. All 24 patients surviving the initial hospitalization were available for follow-up.

Fourteen of the 24 patients died one to 25 months (average 9.2 months) after discharge. Ten patients died of pump failure and one each of reinfarction, arrhythmia, cerebral hemorrhage, and hypovolemic shock. The ten survivors at last follow-up have been followed for 15 to 32 months (average 24 months). Five patients remain in Class II heart failure, four in Class III, and one in Class IV (New York Heart Association classification) at the time of last follow-up. Actuarial survival rate is shown in figure 3. Projected 24 months survival in these patients is 28%.

Discussion

Immediate Prognosis During Vasodilator Therapy

That vasodilator therapy can improve left ventricular performance by reducing systemic vascular resistance, a major part of the total resistance against which the left ventricle operates as a pump, has been documented. This study demonstrates that vasodilator therapy is effective in improving left ventricular performance in patients with acute myocardial infarction, even in the presence of severe pump failure. Cautious use of vasodilators improved left ventricular function in almost all patients with an increase in C.I., SVI, and SWI along with a decrease in LVFP. This hemodynamic and clinical improvement could be maintained with continued use of vasodilators and serious complications did not occur during prolonged use of intravenous

CUMULATIVE SURVIVAL

FiguRE 2. Influence of vasodilator therapy on the hospital mortality in relation to the initial stroke work index. Of patients with SWI between 11-20 g-m/m², 32% died. In contrast, of those with SWI of 10 g-m/m² or less, 82% died.

FiguRE 3. Cumulative survival rate in patients treated with vasodilators for severe pump failure complicating myocardial infarction. At 24 months cumulative survival rate was 28%.
vasodilator therapy (up to 27 days). The mechanism of sudden hypotension without increasing the maintenance infusion rate of nitroprusside in three patients may have been due to uneven flow through a peripheral vein influenced by changes in position of the limb. The fact that such a complication can occur emphasizes the necessity of constant supervision and monitoring of arterial pressure. The present study also suggests that vasodilator therapy may improve the immediate prognosis in patients with severe pump failure complicating myocardial infarction. Thus 24 of the 43 patients survived and were discharged from the hospital. Furthermore, in four of 19 patients who died, the cause of death was not refractory pump failure. Admittedly, the efficacy of vasodilator therapy compared to conventional therapy in improving the immediate prognosis of patients with severe pump failure complicating myocardial infarction cannot be firmly established without a matched control study. However, recent studies in patients with acute myocardial infarction have demonstrated that with conventional therapy, the mortality from pump failure is directly proportional to the severity of depression of cardiac performance.\textsuperscript{12, 14, 15}

In patients with SWI of 20 g-m/m\textsuperscript{2} or less and LVFP of 15 mm Hg or more, the hospital mortality with conventional therapy alone approaches 80%.\textsuperscript{13} In this study, total hospital mortality of 44% with additional vasodilator therapy therefore compared favorably. Scheidt et al.\textsuperscript{14} reported 76% mortality in patients with cardiac work index (CWI) of 1.75 kg/min/m\textsuperscript{2} or less, and 72% mortality when SWI is 20 g-m/m\textsuperscript{2} or less. In this study of 34 patients with cardiac work index of less than 1.75 kg/min/m\textsuperscript{2}, 17 patients (50%) survived and although all patients had SWI of 20 g-m/m\textsuperscript{2} or less, 24 (55.8%) survived. It is to be noted, however, that Scheidt et al.\textsuperscript{14} used mean systolic arterial pressure (MSP) instead of AP and left ventricular end-diastolic pressure (LVEDP) instead of PCW for calculations of cardiac work and stroke work index. Calculated CWI and SWI values with the use of AP as in this study tend to be lower than the values calculated with MSP. On the other hand, in the high levels of LVEDP, PCW is usually lower than LVFP. Therefore, calculated CWI and SWI based on PCW tend to be higher than when these parameters are calculated based on LVEDP.

It is unlikely, therefore, that there would have been any significant difference in derived CWI and SWI values in these patients if these parameters were calculated with the use of MSP and LVEDP instead of AP and PCW. It seems reasonable, therefore, to use the prognostic indicators as advocated by Scheidt et al.\textsuperscript{14} to evaluate the results of vasodilator therapy in this study. Furthermore, Biefl et al.\textsuperscript{15} calculating SWI, based on the same hemodynamic parameters as in this study, reported an 80% mortality in patients with SWI/LVFP index of 1.2 or less. In the present study, even though all patients had SWI/LVFP index of 1.0 or less, the mortality was 44%. Rackley and Russell\textsuperscript{14} reported 100% mortality in patients with clinical cardiogenic shock, a cardiac index less than 2.3 L/min/m\textsuperscript{2}, and LVFP higher than 15 mm Hg. In the present study, 17 patients satisfied the above criteria and their mortality was 53%. These findings therefore suggest that vasodilator therapy may decrease the initial mortality in patients with acute myocardial infarction complicated by pump failure. However, when the SWI is extremely low (\(\leq 10\) g-m/m\textsuperscript{2}) with elevated LVFP, the initial mortality still remains very high (82%) despite vasodilator therapy. Thus it appears from the present study, that (in terms of improving the immediate prognosis) vasodilator therapy is most likely to be effective in patients with an initial SWI of more than 10 g-m/m\textsuperscript{2} and a high LVFP.

**Late Prognosis**

This study also demonstrates that the long-term prognosis in the patients who survived and were discharged from the hospital remains unfavorable. Fourteen patients died in the follow-up period and the cumulative survival at 24 months was 28%. Most patients died of uncontrolled pump failure (71%). Five of the ten late survivors also remain in severe pump failure. Sublingual isosorbide dinitrate has been found useful in improving left ventricular performance in patients with chronic congestive heart failure. Myocardial oxygen consumption also decreases in these patients during isosorbide dinitrate therapy, presumably due to associated reduction in preload and afterload.\textsuperscript{13} It can be hypothesized, therefore, that chronic vasodilator therapy might be useful in patients with pump failure due to ischemic heart disease, not only in improving the mechanical performance but also in maintaining the metabolic function of the ventricle. Although the majority of patients were taking sublingual isosorbide dinitrate along with conventional antifailure therapy, the therapy was not rigidly controlled. The hemodynamic effects of sublingual isosorbide dinitrate last approximately 90 min,\textsuperscript{13} but most patients in this study were using isosorbide dinitrate every 4–6 hours. Whether rigid control of long-term vasodilator therapy could have improved the prognosis in these patients cannot be determined.

Some of these patients might have had resectable localized ventricular aneurysm contributory to refractory heart failure. Whether early investigation for detection of localized ventricular aneurysm and aneurysmectomy can improve long-term prognosis in some of these patients who survive severe pump failure with vasodilator therapy remains speculative.

It is likely, however, that refractory heart failure in these patients is the consequence of extensive myocardial necrosis at the onset of infarct and the amount of remaining functional myocardium is too little to support life for any length of time. Whether suggested new therapeutic approaches\textsuperscript{17} for the preservation of ischemic myocardium at the onset of infarct can improve long-term prognosis in these patients remains to be seen. It is apparent, however, that even though some improvement in initial mortality can be achieved with vasodilator therapy, with or without conventional therapy, the long-term prognosis in patients with severe pump failure complicating myocardial infarction remains unfavorable.

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Left Ventricular Function and Adrenergic Hyperactivity before and after Saphenous Vein Bypass

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SUMMARY Forty patients with severe angina pectoris were studied before and two weeks after saphenous vein bypass surgery (SVG) in order to assess the effect of this operation on left ventricular performance as judged by systolic time intervals (STI). The patients were divided into two groups: group I included 29 patients in whom no postoperative infarction occurred and group II was composed of 11 patients with postoperative infarction. For group I the preop PEP/LVET was 0.39 ± 0.01 preop and slightly but significantly increased to 0.42 ± 0.004 (P<0.025) two weeks postop. The mean preop PEP/LVET was 0.33 ± 0.01 for group II and dramatically increased to 0.54 ± 0.02 (P<0.001) after surgery.

Another striking abnormality was a marked shortening of electro-mechanical systole (QS), which was uniformly present in the postoperative studies. Follow-up studies in 16 patients and urinary catecholamine determination in five patients suggested excessive adrenergic activity was responsible for the abbreviated QS.

This phenomenon must be considered when interpreting the results of SVG on left ventricular function.

IT IS WELL DOCUMENTED that saphenous vein bypass has a beneficial effect upon angina pectoris but there is no universal agreement concerning its effect upon left ventricular performance. Improvement, lack of improvement, and deterioration in left ventricular performance following saphenous vein bypass surgery all have been reported.1-11

In an effort to help resolve these questions we have studied 40 patients undergoing elective saphenous vein bypass surgery for angina pectoris. The systolic time intervals were used to evaluate left ventricular performance before and after surgery. In the course of the investigation it became apparent that excessive adrenergic activity was influencing our measurements. This was particularly true in the early postoperative period. Thus we have also specifically addressed this aspect of the problem in order to determine what role it might play in producing the conflicting results of prior investigations.

Material and Methods

Forty patients undergoing elective saphenous vein bypass for angina pectoris were studied. All subjects underwent preoperative coronary arteriography and quantitative left ventriculography.10,11 Twenty-two of the patients also underwent postoperative catheterization two weeks after surgery. Six patients were receiving digitalis during the study. The mean age of the patients was 51 years. There were 34 males and six females. Preoperatively all were Functional Class III or IV because of angina. Fifteen had had one or

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