Ambulatory Long-term Vasodilator Therapy for Chronic Refractory Heart Failure: Hemodynamic Evaluation and Clinical Response

SATOSHI SAITO, M.D., MASAYUKI ICHIKAWA, M.D., YUKIO OZAWA, M.D.
SEI YUMIKURA, M.D., MASAKI NAGASAWA, M.D.
KAZUHIRA HIBIYA, M.D., YASUO TAMURA, M.D.
KENTARO TOMOBE, M.D. AND MICHINOBU HATANO, M.D.

We evaluated long-term combined vasodilator therapy (hydralazine or ecarazine + isosorbide dinitrate) in 29 patients with chronic congestive heart failure resistant to the optimal conventional therapy. There were 24 men and 5 women, aged 28 to 76 years (mean 52 y/o). The etiology of heart failure was congestive cardiomyopathy in 24 patients, ischemic cardiomyopathy in 4 patients and advanced mitral regurgitation due to calcified mitral annulus in 1 patient. There were 21 patients in NYHA class III and 8 patients in NYHA class IV. All patients continued their previous therapeutic regimen during the period of this study. Hemodynamic measurements were performed with a triple lumen flow-directed balloon-tipped catheter in 20 patients to evaluate the effects of vasodilator therapy. In the rest of 9 patients, heart rate, blood pressure, chest X-ray examination for heart size (CTR) and M-mode echocardiograms for ejection fraction (EF) were monitored. The hemodynamic responses to the combined vasodilator therapy in 20 patients showed significant decreases in afterload and preload concomitant with an increase in cardiac output. The noninvasive evaluation of combined vasodilator therapy in 9 patients resulted in significant improvement in CTR and EF. We also noted a significant improvement in their symptoms of 29 patients. Side effects and drug toxicity were uncommon during vasodilator therapy. It is concluded that the combined vasodilator therapy is most useful adjunctive therapy in the management of severe refractory heart failure. Moreover, long-term nonparenteral vasodilators can be administered even at outpatient clinic without hemodynamic monitoring.

In recent years vasodilator therapy has gained increasing popularity and widespread acceptance in the management of patients with congestive heart failure resistant to the conventional therapy. Many studies have documented the hemodynamic efficacy of this approach, and several have shown that hemodynamic improvement persists for at least several months. In this study, we evaluated long-term follow-up (4 months-5 years: average 2.3 yrs) treated with the combined oral hydralazine or ecarazine hydrochloride and isosorbide dinitrate for chronic refractory heart failure.

Key Words:
- Chronic refractory heart failure
- Vasodilator therapy
- Hydralazine
- Isosorbide dinitrate

MATERIALS

We selected 29 patients with severe chronic congestive heart failure resistant to the optimal conventional therapy with digitalis and diuretics.

The 2nd Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan
Mailing address: Satoshi Saito, M.D., The 2nd Department of Internal Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173, Japan

350 Japanese Circulation Journal Vol. 48, April 1984
TABLE I  HEMODYNAMIC RESPONSES TO COMBINED VASODILATOR THERAPY IN 20 PATIENTS WITH REFRACTORY HEART FAILURE

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>C + V</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR: beats/min</td>
<td>98.1 ± 3.67</td>
<td>94.3 ± 3.76</td>
</tr>
<tr>
<td>MBP: mmHg</td>
<td>92.8 ± 2.26</td>
<td>85.3 ± 2.28</td>
</tr>
<tr>
<td>CI: liters/min/m²</td>
<td>1.93 ± 0.12</td>
<td>3.17 ± 0.17*</td>
</tr>
<tr>
<td>PAW: mmHg</td>
<td>32.4 ± 1.74</td>
<td>20.8 ± 1.99*</td>
</tr>
<tr>
<td>MRA: mmHg</td>
<td>13.3 ± 1.20</td>
<td>7.47 ± 1.0*</td>
</tr>
<tr>
<td>SVI: ml/beat/m²</td>
<td>20.3 ± 1.57</td>
<td>33.2 ± 1.45*</td>
</tr>
<tr>
<td>SWI: g·m/beat/m²</td>
<td>16.6 ± 1.63</td>
<td>28.9 ± 1.88*</td>
</tr>
<tr>
<td>TPR: dynes·sec/cm²</td>
<td>2305 ± 235</td>
<td>1295 ± 83*</td>
</tr>
</tbody>
</table>

C = Control; C + V = Control + Vasodilators; mean ± SEM, *p < 0.01

Abbreviation: HR = heart rate; MBP = mean blood pressure; CI = cardiac index; PAW = pulmonary arterial wedge pressure; MRA = mean right atrial pressure; SVI = stroke volume index; SWI = stroke work index; TPR = total peripheral resistance

There were 24 men and 5 women, aged 28 to 76 years (mean 52 y/o). The etiology of heart failure was congestive cardiomyopathy in 24 patients, ischemic cardiomyopathy in 4 patients and advanced mitral regurgitation due to calcified mitral annulus in 1 patient. Symptoms persisted despite a daily maintenance dose of digoxin and furosemide in average daily dose of 160 mg. There were 21 patients in New York Heart Association (NYHA) class III and 8 patients in NYHA class IV.

METHODS

1) Hemodynamic measurements:

Right heart catheterization was performed with a triple lumen flow directed balloon-tipped catheter through which measurements of right atrial (RA), pulmonary arterial and pulmonary arterial wedge pressure (PAW) were made. Cardiac output (CO) measurements, performed in triplicated with the thermodilution technique using the same catheter, exhibited less than 10% variation. Cardiac output was determined with a bedside Kimray cardiac computer (Model 3500E). Arterial blood pressure was measured from cuff readings and the mean arterial blood pressure (MBP) was estimated from the formula: MBP = D + (S – D)/3, where S is the peak sys-

Fig.1. Hemodynamic responses to combined vasodilator therapy in 20 patients with refractory heart failure.
C: Control (Digitalis + Diuretics)
C + V: C + Vasodilators

Japanese Circulation Journal  Vol. 48, April 1984
tolic and D the peak diastolic pressure.
Derived hemodynamic variables were calculated as follows: Cardiac index (CI) = CO/body surface area (BSA) (liters/min/m²)
Stroke volume index (SVI) = CO/HR/BSA (ml/m²)
Stroke work index (SWI) = SVI x (MBP – PAWP) x 0.0136 (g·m/beat/m²)
Total peripheral resistance (TPR) = 80 x (MBP – MRA) / CO (dynes·sec·cm⁻⁵)

2) Hemodynamic evaluation of vasodilator therapy:
All patients continued their previous therapeutic regimen during the period of hemodynamic evaluation. After baseline hemodynamic measurements were obtained, 20 patients were given both hydralazine or ecarazine hydrochloride (180–300 mg/day) and isosorbide dinitrate (20–60 mg/day) orally. All patients underwent repeat right heart catheterization after 3 to 4 weeks of continuous therapy.

3) Hydralazine or ecarazine and isosorbide dinitrate administration:
Both 60 or 90 mg of hydralazine or ecarazine and 5 or 10 mg of isosorbide dinitrate were administrated three or four times daily.

4) Non-invasive evaluations:
In the rest of 9 patients, the following measurements were obtained before and at approximately 4 months after the combined therapy; Heart rate (HR), blood pressure (BP), chest X-ray examination for heart size (CTR) and M-mode echocardiograms for ejection fraction (EF).

5) Long-term therapy:
All patients continued to receive long-term therapy with combined vasodilator therapy for 4 months to 5 years (average 2.3 years). The results and side effects of this therapy were evaluated from the patient’s subjective responses, the physician’s functional evaluation and analysis.

Fig. 3. Chronic effects of combined vasodilator therapy on MBP, HR, CTR and EF in 9 patients with congestive heart failure. MBP = mean blood pressure; HR = heart rate; CTR = cardiothoracic ratio; EF = ejection fraction.
of variance and the t-test for paired data were used in the statistical analysis of the results.

RESULTS

1) Hemodynamic measurements:

The hemodynamic responses to the combined vasodilator therapy in 20 patients are presented in Table I, Fig. 1 and Fig. 2. The evaluated control total peripheral resistance significantly diminished with increases in CI and SVI.

The parameters of preload, mean right atrial and pulmonary arterial wedge pressure decreased significantly. Left ventricular SWI increased significantly with combined vasodilator therapy. The ventricular function curve shown in Fig. 2 illustrates the different effects of nitrate and hydralazine and the dramatic overall improve-

*Japanese Circulation Journal Vol. 48, April 1984*
ment in left ventricular performance.

2) Chronic effects on BP, HR, CTR and EF:
   The effects of long-term combined vasodilator therapy in 9 patients are shown in Fig. 3.
   There was no significant change in MBP. HR changed significantly from 105.82 ± 5.99 to
   88.82 ± 4.34 beats/min ($p < 0.01$). Furthermore, significant changes in CTR (64.0 ± 6.04 to
   51.6 ± 5.1%, $p < 0.001$) and EF (33.31 ± 14.4 to
   46.93 ± 12.0%, $p < 0.01$) were observed. Representative cases are shown in Fig. 4 and 5.

Case 1. S.K. 54 y/o male, Congestive cardiomyopathy
   Symptoms and chest X-ray findings did not improve and rather worsened during the con-
   ventional therapy. The combined vasodilator therapy resulted in a significant improvement
   in CTR and EF as shown in Fig. 4.
Case 2. K.S. 74 y/o female, Congestive cardiomyopathy
   The cessation of the combined vasodilator therapy caused a deterioration of symptoms and chest X-ray findings. The combined vasodilator therapy was started again and significantly improved these abnormalities without tolerance.

3) Symptomatic improvement:
   We observed that 29 patients treated with combined vasodilator therapy experienced sig-

Change in NYHA functional classification.

<table>
<thead>
<tr>
<th>Class III ($n=21$)</th>
<th>Class I ($5$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IV ($n=8$)</td>
<td>Class II ($16$)</td>
</tr>
</tbody>
</table>

Fig. 6. Effects of chronic vasodilator therapy on the New York Heart Association (NYHA) functional classification in 29 patients with refractory heart failure.

4) Adverse reactions to vasodilator therapy:
   Side effects and drug toxicity were uncommon during vasodilator therapy. One patient
developed positive LE phenomenon. Hydralazine was discontinued and ecarazine hydrochloride
was administered. Thereafter, repeated sero-
logical test showed negative LE phenomenon. Mild headache resulted from the use of nitrates

*Japanese Circulation Journal Vol. 48, April 1984*
in some patients, which did not require discontinuation.

DISCUSSION

Pathophysiologic consequences and clinical manifestations of "Cardiac pump failure" can be related to reduced cardiac output and elevated pulmonary and systemic venous pressures. The major objectives of therapy for pump failure, therefore, are to improve cardiac output and decrease venous pressures. Cardiac output can be improved by decreasing systemic vascular resistance, one of the major factors that play an important role in the regulation of cardiac performance. Increased systemic vascular resistance decreases left ventricular forward stroke and increases end-diastolic volume. Increased end-diastolic volume is also accompanied by an increased end-diastolic pressure that is translated to an elevated pulmonary arterial wedge pressure. Therefore, vasodilator therapy should be beneficial in the management of such patients with both acute and chronic pump failure, particularly, being resistant to the conventional therapy. A decreased systemic vascular resistance is associated with an increase in stroke volume and cardiac output. Furthermore, the venous pooling effect, due to an increase in peripheral venous capacitance, may contribute to a reduction in ventricular volume and pressure. Therefore, the two major objectives of the treatment of pump failure – improvement in forward output and decrease in pulmonary venous pressure – can be achieved. In patients with chronic refractory heart failure, vasodilator such as nitroprusside, prazosin, phenolamine, hydralazine and nitrates gained popularity and have been used with beneficial hemodynamic and clinical effects.

Our study has demonstrated that drugs that directly relax arteriolar smooth muscle, such as orally administered hydralazine or ecarazine, caused a predominant reduction in afterload, thereby improving cardiac output, which we observed in our patients treated with a single oral dose of 60 to 90 mg. However, it has been reported that there was a little change in ventricular filling pressure. An optimal approach to the vasodilator therapy of chronic refractory heart failure with the agents now available would be to combine drugs with relatively selective effects on the venous capacitance and the arteriolar resistance vessels. Pierpont et al. recently investigated this approach by measuring the hemodynamic response in combination with isosorbid dinitrate? They found that the combination produced both an increase in cardiac output and a reduction in left ventricular pressure. Our study also demonstrated that isosorbid dinitrate produced a significant decrease in right atrial and pulmonary arterial wedge pressures. Our data also confirm the predominant effect of nitrates on the venous capacitance vessels and thus their selective effect on preload in patients with heart failure. The striking and potentially most important finding of these study is that the beneficial hemodynamic effects of these two drugs were additive. The ventricular function curve shown in Fig. 2 illustrates the differing effects of nitrates and hydralazine and the dramatic overall improvement in left ventricular performance produced with combined therapy. These findings suggest that the combined use of hydralazine and isosorbid dinitrate can be the goal of treatment to alleviate the symptoms of heart failure.

Long-term nonparenteral vasodilator can be administered even at outpatient clinic without hemodynamic monitoring. In these cases, M-mode echocardiogram (EF) and chest X-ray (CTR) could be of value in assessing cardiac response to the vasodilator therapy. Combined therapy with nonparenterally administered nitrates and orally administered hydralazine is relatively convenient because the nitrates can be administered at intervals of up to 6 hours and hydralazine may be given every 8 hours. This form of therapy was well tolerated in our patients. Although drug-induced lupus is a serious potential complication, we observed only one patient who developed a positive serologic test without clinical evidence of lupus erythematosus. Despite the resultant decrease in pulmonary arterial wedge pressure and peripheral resistance, there were no undesirable changes in heart rate or blood pressure. Our patients all experienced subjective and functional improvement, which has persisted for the longest duration of 5 years. The striking improvement following reinstitution of combined vasodilators illustrated in Fig. 5 suggests that the response to these drugs is sustained. Some of our patients, who underwent ambulatory long-term vasodilator, required the reduced dose of diuretic agents, suggesting that the vasodilator therapy is at least in part responsible for the symptomatic improvement in these patients. We concluded that the combined vasodilator therapy is most useful adjunctive therapy in the management of severe
chronic refractory heart failure.

REFERENCES


8. FRANCIOSA JA, PIERPONT G, COHN JN: Hemodynamic improvement after oral hydralazine


