Effect of Prostacyclin and Prazosin in the Treatment of Congestive Heart Failure; with Special Reference on the Sympathetic Nervous System

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Therapy to decrease the load in congestive heart failure is now classified as acute and chronic vasodilator therapy. In this symposium, we presented prostacycline (PG I₂) as an acute and prazosin as a chronic vasodilator. Their hemodynamic and clinical effectiveness were evaluated and their effect on the sympathetic nervous system was also studied.

We studied the effect of intravenous prostacyclin infusion in doses of 22 ± 11 ng/kg/min in nine patients with severe congestive heart failure refractory to digitalis and diuretic drugs. After prostacyclin infusion, mean pulmonary capillary wedge pressure decreased from 21.0 ± 7.9 to 15.0 ± 6.6 mmHg ($p < 0.001$), mean arterial pressure from 98.9 ± 12.8 to 76.2 ± 7.0 mmHg ($p < 0.001$), systemic vascular resistance from 2,574 ± 384 to 1,368 ± 283 dynes·sec·cm⁻⁵ ($p < 0.001$), pulmonary vascular resistance from 1,008 ± 451 to 443 ± 135 dynes·sec·cm⁻⁵ ($p < 0.001$) and pulmonary arteriolar resistance from 330 ± 111 to 189 ± 73 dynes·sec·cm⁻⁵ ($p < 0.001$). The cardiac index increased from 2.0 ± 0.37 to 3.2 ± 0.59 l/min/m² ($p < 0.001$), and the stroke index from 27.6 ± 8.69 to 42.0 ± 0.62 ml/m² ($p < 0.001$). Moreover, prostacyclin therapy counteracted the sensation of coldness of the limbs and face, and patients felt warmth and mild flushing of the face.

The effect of prazosin on the exercise duration time until dyspnea was evaluated by the treadmill test. In comparison with a placebo, prazosin significantly increased this time from 11.4 ± 5.6 min to 13.0 ± 5.8 ($p < 0.005$) and significantly reduced systolic blood pressure from 121 ± 22 mmHg to 114 ± 20 ($p < 0.005$). These data suggest that prazosin is effective in treating chronic left ventricular failure.

The effect of vasodilators on the sympathetic nervous system in congestive heart failure is not known. After prostacyclin therapy, plasma norepinephrine levels did not change significantly (824 ± 375 pg/ml vs 880 ± 468, NS). During chronic therapy with prazosin, plasma norepinephrine levels increased significantly (766 ± 209 pg/ml vs 416 ± 209 with placebo, $p < 0.001$). When mean pulmonary capillary wedge pressure was maintained at

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around 15 mmHg by oral prazosin administration, prazosin increased the plasma norepinephrine level significantly. (384 ± 141 to 450 ± 121 [1 hr, $p < 0.001$], 580 ± 161 [2 hr, $p < 0.001$], 504 ± 98 [3 hr, $p < 0.001$]). These results suggest that the sympathetic nervous system may play an important role in congestive heart failure during both acute and chronic vasodilator therapy.

INOTROPIC agents to increase myocardial contractility and diuretic drugs have been the basic treatment of pump failure. Recently, a variety of vasodilators have been used in the treatment of severe congestive heart failure.¹ Among the various agents, nitroprusside has been the most extensively investigated and widely prescribed. With the production of balanced effects on resistance and capacitance vessels, there is an impedance reduction with increased cardiac output simultaneously with enhanced ventricular emptying and relief of pulmonary congestion. However, extended use of this agent in long-term management may be associated with toxicity due to the accumulation of thiocyanate. Prostacyclin is a recently discovered biologically active prostaglandin that has platelet antiaggregating and vasodilating activities.² We used prostacyclin to dilate the vessels of patients with severe congestive heart failure who were already receiving full doses of digitalis and diuretics.

Prazosin, a recently introduced oral vasodilator with balanced venous and arterial effects has been used to treat patients in chronic heart failure, because the hemodynamic effects of this drug are similar to those of nitroprusside.³ We performed a singleblind study to evaluate the effect of prazosin on treadmill exercise performance in patients with chronic congestive heart failure.

Norepinephrine is the neurotransmitter of the sympathetic nerves, and the plasma level of norepinephrine is believed to reflect the level of sympathetic nervous activity.⁴ In congestive heart failure, there is an augmentation of sympathetic nervous activity reflected by an increase in plasma norepinephrine levels, and this increased adrenergic support seems to play a compensatory role in the maintenance of cardiac performance in the failing heart.⁵ However, the effect of vasodilating agents on sympathetic nervous activity in congestive heart failure remains unknown. Therefore, we studied the activity of the adrenergic system during vasodilator therapy in patients with congestive heart failure.

MATERIALS & METHODS

[Patient Population]

Prostacyclin Therapy

The study group included nine patients with severe congestive heart failure (mean age, 70 years). All patients were in functional class IV according to the criteria of the New York Heart Association (NYHA). Coronary artery disease was diagnosed by a history of documented acute myocardial infarction or by coronary arteriography. All patients continued to have symptoms of cardiac failure at rest while receiving digitalis and diuretic drugs. The usual morning dose of diuretic drugs was administered on the evening before the study, and the usual daily dose of digoxin was ingested on the morning of the study. Prostacyclin therapy was offered to patients whose congestive heart failure could not be controlled by conventional treatment.

Chronic Prazosin Therapy

The group consisted of 7 patients with ischemic heart disease, 6 with dilated cardiomyopathy, and 2 with mitral regurgitation. They all received prazosin for more than one month because of refractory congestive heart failure despite the administration of digitalis and diuretics (mean age 56 years, 6 in NYHA II, 8 in NYHA III and 1 in NYHA IV).

The nature, potential benefits and possible risks were fully explained to the patients, who then gave informed consent.

[Hemodynamic Studies]

We performed right heart catheterization with a triple lumen flow-directed balloon-tipped catheter (Edwards Laboratories, Santa Ana, California) through which measurements of pulmonary arterial and pulmonary capillary wedge pressures were determined. Measurements were made with zero reference level at the mid-axillary line with the patient supine. Cardiac output was determined in triplicate by the thermodilution technique with a bedside computer (9520 A Thermodilution Computer, Edwards Labora-

Fig.1. Protocol for chronic heart failure.

Time	Stage	Speed	Grade
0-3 min	-	1.0 MPH	0 %
3-6	Zero	1.7	0
3-9	One-half	1.7	5
9-12	First	1.7	10
12-15	Second	2.5	12
15-18	Third	3.4	14
18-21	Fourth	4.2	16
21-24	Fifth	5.0	18
24-27	Sixth	5.5	20
27-30	Seventh	6.0	22

Fig.2. Protocol of treadmill test for chronic heart failure.

tories). The heart rate was obtained from a continuously recorded electrocardiogram. Arterial pressure was measured either directly by means of a small catheter in the brachial artery, with the mean determined electronically or by a sphygmomanometer with the mean arterial pressure derived from the formula: mean arterial pressure = $D + (S - D)/3$ where S is the peak systolic pressure and D the end-diastolic pressure. Calculations used to quantify cardiocirculatory variables included: cardiac index = cardiac output/body surface area in square meters, systemic vascular resistance = (mean arterial pressure - right atrial pressure)/cardiac output $\times 80$, pulmonary arteriolar resistance = (mean pulmonary arterial pressure - pulmonary wedge pressure)/cardiac output $\times 80$, pulmonary vascular resistance = mean pulmonary arterial pressure/cardiac output $\times 80$.

[Treadmill Tests]

Figure 1 shows the protocol of treadmill testing for chronic congestive heart failure. Patients performed multistage maximal treadmill exercise tests until the onset of marked dyspnea, approximately 2 hrs after their morning dose of medication (Fig. 2). After more than 4 weeks of prazosin therapy, the first test was performed (Ex. (1)). One week later, the same exercise test was repeated (Ex. (2)), and after one week of placebo administration, the same test was performed again (Ex. (3)). Ex. (2) was compared with Ex. (3). Marked dyspnea was the limiting factor in all maximal treadmill exercise tests in all patients. The patients were monitored simultaneously by with leads, aVf, V2 and V6 throughout exercise. Blood pressures were recorded with a mercury sphygmomanometer. Heart rates were measured from the electro-

Fig.3 Protocol of treadmill test for chronic heart failure.

Fig.4. Effects of prostacyclin of mean arterial pressure and pulmonary capillary wedge pressure.

cardiographic recordings. Fig. 3 shows our treadmill exercise test method (☆), in which we added three steps before the standard Bruce method⁶

[Administration of Drugs]

Prostacyclin Administration

Prostacyclin (PGI₂, Na) (Ono Company) was prepared as a sterile powder and dissolved in a buffer of glycine at pH 10 and diluted to a final concentration of 50 µg/ml. Prostacycline was infused by a microinfusion pump (SP-5, Nipro Company) with a 21 gauge butterfly needle inserted into a forearm vein. It was given initial-

Fig.5. Effect of prostacyclin on cardiac index and stroke index.

ly at a rate of 10 ng/kg/min every 10 minutes until the systolic pressure was lowered by about 15 to 20 percent. The mean constant flow rate of prostacycline was 21 ± 11 ng/kg/min. After 1 hour of constant infusion, hemodynamic variables and blood samples were again obtained.

Chronic Prazosin Therapy

The mean dose given for more than one month until exercise testing was 7.6 mg/day. The average dose of prazosin given during the study was 8.1 mg.

[Plasma Norepinephrine Assay]

Plasma norepinephrine was determined by the high-performance liquid chromatographic method which we developed⁷. Blood samples were drawn from the pulmonary artery into heparinized syringes, transferred into ice-chilled tubes containing sodium metabisulfite (0.5 g/liter) and centrifuged at $1,500 \times g$ for 5 minutes.

[Platelet Aggregation]

Adenosine-diphosphate (3.4 µM)-induced platelet aggregation was determined as previously described⁸.

[Statistics]

Values were presented as mean $\pm$ SD. The multiple comparison test with one way analysis of variance was used. A P value of less than 0.05 was considered significant.

RESULTS

Prostacyclin Therapy

Hemodynamic effects: After prostacyclin

Fig.6. Effect of prostacyclin on systemic vascular resistance, pulmonary vascular resistance and pulmonary arteriolar resistance.

Fig.7. Effect of prazosin and placebo on exercise time.

Fig.8. Effect of prostacyclin infusion on plasma norepinephrine levels.

administration, the control heart rate of 78 ± 21 beats/min increased to 82 ± 24 (NS). Mean arterial pressure decreased from 98.9 ± 12.8 mmHg to 76.2 ± 7.0 ($p < 0.001$) and remained low during the study. The elevated pulmonary capillary wedge pressure of 21.0 ± 7.9 mmHg decreased to 15.0 ± 6.6 ($p < 0.001$) (Fig. 4). The low control cardiac index of 2.0 ± 0.37 liters/min/m² increased to 3.2 ± 0.59 ($p < 0.001$). Similarly, the reduced control stroke index of 27.6 ± 8.69 ml/m increased to $42.0 \pm$

0.62 ($p < 0.001$) (Fig. 5). Systemic vascular resistance, pulmonary vascular resistance and pulmonary arteriolar resistance (dynes·sec·cm⁻⁵) decreased from $2,574 \pm 384$ to $1,368 \pm 283$ ($p < 0.001$), from $1,008 \pm 451$ to 443 ± 135 ($p < 0.001$) and from 330 ± 111 to 189 ± 73 ($p < 0.001$), respectively, (Fig. 6). After prostacyclin therapy was discontinued, the hemodynamic variables began to deteriorate within about 10 minutes and returned to the control levels after 30 minutes.

Fig.9. Effect of prazosin on plasma norepinephrine levels (N = 9, * $p < 0.05$).

The study population for acute prazosin therapy was nine patients with congestive heart failure who had not responded to digitalis and furosemide therapy: mean age 59 years, 6 cases of coronary artery disease, 2 cases of dilated cardiomyopathy, and 1 case of aortic regurgitation, 7 in NYHA III and 2 in NYHA IV. After completion of all baseline values, oral prazosin (35 $\mu\text{g/kg}$ body weight) was ingested as a single dose. All hemodynamic variables and plasma norepinephrine were determined for 3 hrs at 1 hr intervals.

Platelet aggregation: During infusion of prostacyclin, adenosine diphosphate-induced platelet aggregation decreased from 67 ± 24 to 12 ± 7 percent ($p < 0.05$), but it returned to the control level (65 ± 30) within 60 minutes after prostacyclin infusion was terminated.

No patient experienced chest discomfort or other adverse reactions during or after prostacyclin infusion. All patients had mild facial

flushing and complained of warmth of the limbs. Urinary volume increased. None had phlebitis or necrosis of the vessels through which prostacyclin was administered.

Chronic Prazosin Therapy

Prazosin given for one month significantly increased the exercise duration time from 11.4 ± 5.6 min to 13.0 ± 5.8 ($p < 0.05$) (Fig. 7) and significantly reduced the systolic blood pressure from 121 ± 22 mmHg to 114 ± 20 ($p < 0.005$). Diastolic blood pressure did not change significantly.

Plasma Catecholamine Levels

After prostacyclin therapy, the elevated baseline plasma norepinephrine levels did not change (824 ± 375 pg/ml versus 880 ± 468 , NS) (Fig. 8). Changes of plasma norepinephrine levels after acute prazosin therapy are shown in Fig. 9. Prazosin-mediated hemodynamic changes were significantly different from control values except for heart rate. The plasma norepinephrine level rose significantly in all patients as mean pulmonary capillary wedge pressure, mean arterial pressure, mean pulmonary arterial pressure and total systemic resistance declined. During chronic prazosin treatment, plasma norepinephrine levels were significantly higher than during placebo administration (766 ± 209 pg/ml vs 416 ± 209 , $p < 0.001$).

DISCUSSION

The present study shows that prostacyclin can be used to improve the hemodynamic state in congestive heart failure. In each patient, prostacyclin infusion induced a significant reduction in mean arterial pressure as pulmonary capillary wedge pressure decreased, and there were prompt decreases in pulmonary arteriolar resistance, pulmonary vascular resistance, and systemic vascular resistance, with consequent increases in cardiac index and stroke index. Thus this drug is effective in reducing both ventricular preload and afterload, and its action seems to be similar to that of nitroprusside. Whether prostacyclin has an inotropic effect on the failing heart is not known, but the hemodynamic improvement can be explained by its known vasodilating action and resulting unloading effect. The mechanism of action of prostacyclin in producing vasodilation of constricted vessels and the potential roles of prostaglandins in the cir-

culatory abnormalities of congestive heart failure are unknown.

There was neither phlebitis nor necrosis of the peripheral vessels through which prostacyclin was administered. Bleeding did not occur. Platelet aggregation decreased significantly with prostacyclin but returned to the control level after prostacyclin was discontinued.

Vasodilator therapy with prostacyclin may be useful in the management of acute heart failure after acute myocardial infarction because of its platelet antiaggregating properties. It is assumed that prostacyclin can be an alternative to, or even a better vasodilating agent than, nitroprusside, particularly when the required dosage or duration of therapy would be likely to cause thiocyanate toxicity or when nitroprusside is not effective. The unstable character of prostacyclin will be resolved by the development of its stable analogue.

The usefulness of vasodilator therapy in chronic congestive heart failure is still controversial.⁹ However, in this study we found that chronic oral prazosin therapy improved the results of the multistage treadmill exercise test in patients with chronic congestive heart failure.

Increased sympathetic nervous activity has been reported in patients with congestive heart failure.¹⁰ The plasma norepinephrine level was found to correlate directly with the functional cardiac status and reflect the degree of cardiac failure.⁵

In patients with congestive heart failure, there is a depletion of norepinephrine in the myocardium of the failing heart.¹¹ In contrast to decreased levels of cardiac norepinephrine, an increase in the level of plasma norepinephrine is considered to be one of the compensatory mechanisms to increase myocardial contractility and to maintain normal circulation in the failing heart.

The exact mechanism and meaning of norepinephrine increase during vasodilation by prazosin therapy remains unclear. Prazosin acts on vascular alpha 1 receptors and has little effect on alpha 2 receptors.¹² In this regard, prazosin differs from phentolamine, which blocks both alpha 1 and alpha 2 receptors.¹³ The antagonistic action on alpha 2 receptors by phentolamine is considered to be related to enhanced norepinephrine release. However, prazosin may have a weak alpha 2 receptor blocking property, and this property may contribute to an increase in the level of plasma norepinephrine. The second

possibility is that a systemic reflex mechanism, such as a baroreceptor reflex, could function in such a way as to counteract the mechanical vasodilation induced by prazosin, resulting in an increase in plasma norepinephrine levels. Despite the elevation of plasma norepinephrine levels during vasodilation, the absence of an increase in heart rate may be attributable to a diminution in the responsiveness of the heart to the elevated levels of norepinephrine in congestive heart failure. In our previous study, we reported that the acute hemodynamic improvement by nitroprusside therapy in congestive heart failure was associated with the increased plasma norepinephrine elevation.¹⁴ The pharmacological action of nitroprusside is direct relaxation of vascular smooth muscle in both arterioles and veins and there is no direct action on norepinephrine efflux. Thus, the mechanism is considered as a baroreceptor reflex. Lack of the elevation of plasma norepinephrine levels by prostacyclin infusion might be due to the net effect of both baroreceptor reflex and inhibitory effect on the sympathetic nervous system.¹⁵

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