Radionuclear Measurement of Peripheral Hemodynamics in Selection of Vasodilators for Treatment of Heart Failure

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In order to select the optimal vasodilator for the treatment of patients with congestive heart failure (CHF), the acute effects of three vasodilators (isosorbide dinitrate (ISDN) 5 mg, nifedipine 10 mg, and prazosin 1 mg) on peripheral capacitance and resistance vessels (CV and RV) were evaluated by a newly devised radionuclear technique (Study 1). Thirty-six patients with chronic CHF were divided into Group A (ejection fraction (EF) ≧ 35%, n = 20, mean EF: 47.2 ± 6.5%) and B (EF < 35%, n = 16, mean EF: 24.8 ± 7.1%). ISDN produced the strongest CV dilatation (25% in both groups). Nifedipine reduced RV tone in Groups A and B (14% and 27%, respectively), and CV tone in Group A (6%). Prazosin had the most prominent effects on both vessels in Group B. From these results, it appeared: (a) ISDN is indicated for the cases with increased CV tone, (b) nifedipine is suitable for those with increased RV tone, (c) in cases of increased tone in both vessels, nifedipine (when EF ≧ 35%) or prazosin (when EF < 35%) is optimal. To evaluate the validity of this assignment, 49 subjects with CHF were divided into Group 1 (n = 16, increased CV tone), Group 2 (n = 17, increased RV tone), and Group 3 (n = 16, increased CV and RV tone) in Study 2. In Group 1, the changes of all indexes were not significantly different between the subjects treated with optimal drug based on the assignment (subgroup P) and those with a non-optimal drug (subgroup N) after 2 wk of therapy. In Group 2, however, improvements of RV tone, EF, and exercise duration in subgroup P were greater than those in subgroup N (31 versus 10%, 21 versus 0%, 41 versus 14%, respectively). In Group 3, the results were the same as in Group 2 (34 versus 19%, 24 versus 8%, 26 versus 9%). These findings suggested that the selection of the optimal vasodilator based on peripheral hemodynamic evaluation with a newly devised radionuclear technique permits more effective treatment of chronic CHF.

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The usefulness of vasodilation therapy in chronic congestive heart failure has been sufficiently established by a number of reports (*1–16*), and various vasodilating agents with diverse mechanisms of action are currently in clinical use. However, there is no agreement on how to select the most appropriate vasodilating agent for individual patients with heart failure. Vasodilating agents for heart failure are selected by various methods. The disease is classified into several subsets on the basis of hemodynamic evaluation by invasive techniques and appropriate drugs are assigned to each of the subsets, or the causes of increases in vascular tone are explored in relation to neurohumoral factors, and antagonists to the responsible neurohumoral factors are selected. However, a number of problems must be solved before these methods achieve general acceptance.

We devised a new method to quantitatively and noninvasively evaluate peripheral hemodynamics using erythrocytes labeled with technetium-99m (^{99m}Tc) (*17*). This method readily allows assessment of the extent of the increase in vascular tone in the capacitance and resistance vessels (CV and RV) in patients with heart failure, and the results correlated well with those of central hemodynamic measurement.

Peripheral hemodynamics in congestive heart failure varies with the severity of the condition. This leads to differences in the responses of peripheral vessels to the same vasodilating agent according to the severity of the disease (*10*). Therefore, we first investigated the acute effects of a single administration of three vasodilators, namely isosorbide dinitrate, nifedipine, and prazosin,

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on CV and RV in patients with mild and severe heart failure (Study 1).

Based on the results of measurements of peripheral hemodynamics in this study, we grouped the patients into three categories (those showing increased tone in CV, RV, or both vascular systems), and assigned a drug considered to be optimal to each of the groups. To examine the validity of this assignment, we divided each group into two subgroups. One subgroup was composed of the patients administered a preferable drug, and the other group received a nonpreferable drug. We compared cardiac and peripheral hemodynamic indexes between these two subgroups after 2 wk (Study 2).

Such investigation about the selection of vasodilating agents using a new technique for peripheral hemodynamic measurement is unprecedented, and is expected to open up new possibilities in vasodilation therapy for heart failure.

MATERIALS AND METHODS

Study 1

The subjects were 36 patients with New York Heart Association class II or III chronic congestive heart failure for at least 1 mo treated with digitalis or diuretics (Table 1). These patients were divided according to ejection fraction (EF) values as an index of global cardiac function into those with mild heart failure (Group A) and those with severe heart failure (Group B). An EF value of 35% was considered to be an appropriate cutoff value for classification between mild and severe heart failure (*18*). Accordingly, Group A consisted of the patients with EF values of 35% or above, and Group B with EF values lower than 35% (Table 1). Mean EF (± s.d.) was 47.2 ± 6.5% in Group A and 24.8 ± 7.1% in Group B ($p < 0.001$). Informed consent was obtained from all patients.

The agents were administered at a dose of: 5 mg sublingually for isosorbide dinitrate, 10 mg sublingually for nifedipine and 1 mg orally for prazosin. The following hemodynamic indexes were evaluated before the administration and at the time when the treatment showed the greatest effects (15, 30, and 120 min after the administration of isosorbide dinitrate, nifedipine, and prazosin, respectively). The tests were carried out 2 or 3 hr after breakfast, and different drugs were tested in the same subjects on different days under identical conditions.

TABLE 1
Clinical Characteristics of Subjects in Study 1

Group	Criterion	Total number	Age (mean ± s.d.)	EF (mean ± s.d.)	Diagnosis CAD*	DCM†
A	EF‡ ≧ 35%	20	62.7 ± 10.3	47.2 ± 6.5	13	5
B	EF > 35%	16	55.5 ± 11.8	24.8 ± 7.1	6	5

* CAD: Coronary artery disease
† DCM: Dilated cardiomyopathy
‡ EF: Ejection fraction

Erythrocytes were labeled in vivo with ^{99m}Tc (^{99m}Tc dose, 0.1 mCi/kg) according to the methods of Pavel et al. (*19*). ECG-gated radionuclide cardiac pool images were obtained with a GE Maxicamera 400 A/T (General Electric, Milwaukee, WI) equipped with a parallel-hole collimator from a modified 40°-LAO position, and EF was calculated with a GE Maxister dataprocessing system. Immediately thereafter, peripheral hemodynamics were evaluated by our radionuclear technique previously reported (*17*).

The subject was placed in the supine position with the left upper limb slightly away from the body at the level of the midaxillary line. An arterial occlusion cuff was placed around the arm just above the wrist joint and a venous occlusion cuff just above the elbow joint. A scintillation detector (equipped with a flat-field collimeter) to measure dynamic functions was positioned as closed to the forearm as possible. The end of the collimator was rectangular (11 × 7 cm). The detector-rate mator was connected to a computer. The measurement was started after the confirmation of the stability of radioactivity in the forearm. Arterial occlusion was maintained throughout the measurement with a cuff pressure of 200 mmHg. The sampling time was 5 sec. One minute after commencement of measurement, the venous occlusion cuff was rapidly inflated to 40 mmHg. Radioactivity in the forearm started to increase and finally reached a plateau usually in 3 to 5 min. The results of measurement were stored in a computer. During this time, blood pressure was recorded every minute by an automatic blood pressure recorder on the opposite arm. When the measurement was completed, a 1-ml sample of blood was taken, and its radioactivity was counted by the same detector for the conversion of radioactivity to blood volume. The volume in the monitored forearm segment was measured using a large capacity measuring cylinder. After the attenuation and decay correction, the various peripheral hemodynamic indexes were calculated from these data. Forearm blood volume (FBV; ml/100 ml) indicated the volume of blood per 100 ml of tissue (prior to venous occlusion) in the measured arm. Venous capacity index (VCI; %) was expressed as the percentage of FBV to the volume of blood at the plateau level after venous occlusion. Forearm blood flow (FBF; ml/100 ml/min) indicated the blood flow per minute in the same region, and forearm vascular resistance (FVR; mmHg/ml/100 ml/min) was calculated by dividing the mean arterial pressure (diastolic pressure plus one-third of pulse pressure) by forearm blood flow. We regarded the mean ± 1 s.d. of peripheral hemodynamic measurement by this technique in 35 normal subjects (VCI: 63.8 ± 5.5%, FVR: 24.3 ± 5.1 mmHg/ml/100 ml/min) as the normal range. Based on these results, patients with VCI values of 70% or above were considered to have increased CV tone, and those with FVR of 30 mmHg/ml/100 ml/min or above to have increased RV tone.

Vasodilating properties of three agents on CV and RV were assessed by comparing the mean percent changes of the variables after the administration of each agent.

The differences between the values before and after the administration within the same group were tested statistically by paired t-test, and the differences of mean percent changes among the groups were examined by an analysis of variance. Whenever such analysis indicated the presence of significant intergroup variability, subsequent comparisons between groups performed by Scheffe's multiple comparisons method.

Thereafter, we classified the subjects with chronic heart failure into three groups according to their peripheral hemodynamic characteristics: Group 1 with increased CV tone, Group 2 with increased RV tone, and Group 3 with increases in tone of both vascular systems. Furthermore, we proposed the criteria for selection of preferable vasodilator for each group of patients based on the vasodilating property of the agents.

Study 2

The validity of the criteria proposed in Study 1 for determination of preferable choice of drug was examined by comparing changes in various indexes between the subjects treated with the preferable drug and those with nonpreferable drug 2 wk after the treatment.

Forty-nine patients with chronic congestive heart failure for at least 1 mo were studied and informed consent was obtained from all patients. These subjects were classified into three groups indicated above (Table 2).

The subjects in each group were further divided into subgroup P which was treated with the preferable drug, and subgroup N which was given one of the two nonpreferable drugs alternately chosen. The choice of the drug was done at random. Subgroup P consisted of eight, seven, and eight patients in Groups 1 to 3, respectively, and subgroup N consisted of eight, ten, and eight for the respective groups.

The doses of digitalis or diuretics already administered were not changed during the study. The doses of the test drugs were: 20 mg/day for isosorbide dinitrate, 40 mg/day for nifedipine, and 3 mg/day for prazosin.

The Bruce modified treadmill test devised by Kojima et al. (*20*) was carried out to evaluate the changes in exercise tolerance. This test was carried out by the symptom-limited maximum exercise technique setting the endpoint at the appearance of dyspnea or general fatigue, and the exercise duration (minutes) and maximum work load (Mets) were determined. The subjects performed the exercise with a light load a few days prior to the initial test to familiarize them with the procedures. No subjects in this study exhibited arrhythmia, chest pain, or ischemic changes on ECG during the test.

Comparisons of the basement values in each indexes among the groups were done by an analysis of variance. Mean percent changes of the variables after 2 wk of treatment were compared between two subgroups in each group using Scheffe's multiple comparisons method.

RESULTS

Study 1

Figure 1 shows the mean percent changes of variables after single administration of three agents. Isosorbide dinitrate produced significant increase of FBV and VCI in both groups, decrease of FBF in Group A, whereas decrease of FVR in Group B. EF significantly increased only in Group B. Blood pressure decreased in both groups.

Nifedipine produced significant increase of FBV and VCI in Group A alone. FBF significantly increased in Group B. FVR and EF improved in both groups, but the changes were greater in Group B. Blood pressure was significantly reduced in both groups.

FBV and VCI were increased significantly in both groups by prazosin. FBF and EF increased and FVR decreased significantly in Group B. Blood pressure decreased in both groups.

Isosorbide dinitrate showed the most prominent dilating effect on CV in both groups among the agents, whereas nifedipine was the only one that produced RV dilatation in both groups. Only nifedipine increased EF in Group A, whereas all drugs were effective in Group B. However, the effect of isosorbide dinitrate was weaker than that of nifedipine or prazosin.

Study 2

Among the three groups, impairment of cardiac function was most prominent in Group 3 (Table 2). There were no significant differences in baseline values of age,

TABLE 2
Clinical Characteristics of Subjects in Study 2

	Group 1	Group 2	Group 3
Characteristics	Preload increased	Afterload increased	Pre- and afterload increased
Number of cases	16	17	16
Mean age	62.8 ± 10.2	60.9 ± 10.3	58.5 ± 12.1
Sex (M:F)	9:7	14:3	11:5
Cause of CHF*			
Coronary heart disease	13	12	12
Dilated cardiomyopathy	3	5	4
Left ventricular ejection fraction (%)	45.7 ± 10.4	38.7 ± 8.6†	29.1 ± 11.3‡
Forearm blood volume (ml/100ml)	7.9 ± 1.3	8.2 ± 1.0	6.6 ± 1.1†
Venous capacity index (%)	72.5 ± 2.0	65.5 ± 2.9†	73.8 ± 2.9‡
Forearm blood flow (ml/100 ml/min)	4.2 ± 0.9	2.5 ± 0.7†	1.9 ± 0.5‡
Forearm vascular resistance (mmHg/ml/100 ml/min)	20.2 ± 2.3	36.6 ± 9.0†	47.1 ± 6.6‡

* CHF = Congestive heart failure.
† $p < 0.05$ in comparison with the value in Group 1.
‡ $p < 0.05$ in comparison with the value in Group 2.

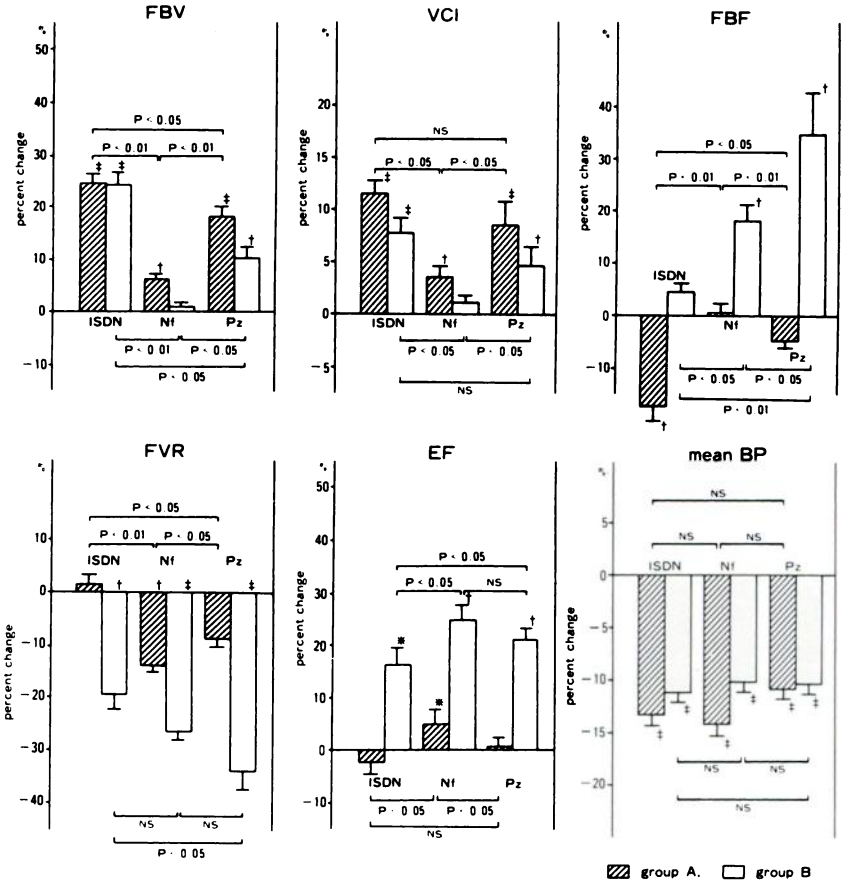

FIGURE 1
Comparisons of percent changes of the variables induced by a single administration of isosorbide dinitrate (ISDN), nifedipine (Nf), and prazosin (Pz). *:$p < 0.05$; †:$p < 0.01$; ‡: $p < 0.001$ in comparison with the control value.

extent of the impairment of cardiac function, or peripheral hemodynamic indexes between any two subgroups in each group (Table 3).

There were no significant differences in percent changes of the indexes between subgroups P and N of Group 1 (Table 3, Fig. 2) after 2 wk of treatment. In Group 2, the percent changes of FBV and VCI, which are indexes of CV, showed no differences between the two subgroups, but those of FBF, FVR, EF, exercise duration, and maximum workload were significantly greater in subgroup P. Similarly, in Group 3, the percent changes in indexes of CV showed no differences, but those of FBF, FVR, EF, exercise duration, and maximum workload were significantly greater in subgroup P.

Individual responses in FVR and VCI are shown in Figure 3. In Group 1, 50% of subjects in both subgroups shifted to normal zone 2 wk after the treatment. In Group 2, all of seven patients in subgroup P, and three of ten in subgroup N moved to normal zone. In Group 3, three of eight patients of subgroup P shifted to normal zone, and only one remained in Group 3. While in subgroup N, none of eight patients shifted to normal zone, and five subjects remained in the category of Group 3. Accordingly, marked differences in the peripheral hemodynamic responses were seen between two subgroups in Groups 2 and 3.

DISCUSSION

Study 1

Isosorbide dinitrate is generally considered to have vasodilating effects on CV (*21–24*), nifedipine to have the same effects on RV (*5,25–28*), and prazosin to have similar effects on both systems (*29–32*). In this study, isosorbide dinitrate showed vasodilating actions on CV, regardless of the extent of the impairment of cardiac function, and on RV in patients with severe impairment (Fig. 1). Leier et al. (*4*) and Pouleur et al. (*33*) observed a reduction in total systemic vascular resistance as well as in pulmonary capillary wedge pressure after a single administration of isosorbide dinitrate. Our finding that isosorbide dinitrate induced a reduction in FVR also in Group B suggests that the agent has vasodilating effects on both vascular systems. No changes in RV were observed in Group A, probably because CV under diuretic therapy was further dilated by the administration of isosorbide dinitrate. This may have led to reductions in venous return and cardiac output, which resulted in a marked reduction in blood pressure. This reduction in blood pressure is considered to have induced an increase in RV tone due to sympathetic baroreflex, masking the direct vasodilating effects of the agent. In Group B, on the other hand, many patients did not respond to diuretic therapy. They showed elevated left ventricular

TABLE 3
Values Before and After Treatment in Subgroup P and N of Groups 1–3

	Group 1				Group 2				Group 3			
	Subgroup P		Subgroup N		Subgroup P		Subgroup N		Subgroup P		Subgroup N	
	Pre*	2W†	Pre	2W	Pre	2W	Pre	2W	Pre	2W	Pre	2W
Forearm blood volume (ml/100 ml)	8.4 ± 1.3	10.0 ± 1.5§	7.5 ± 1.3	8.8 ± 1.3§	7.9 ± 1.0	8.2 ± 1.3	8.4 ± 1.1	8.9 ± 1.3	6.6 ± 1.0	7.4 ± 1.0‡	6.5 ± 1.1	7.3 ± 1.3‡
Venous capacity index (%)	72.9 ± 1.9	69.1 ± 2.3§	72.1 ± 2.2	68.1 ± 3.7§	65.0 ± 3.0	62.3 ± 2.8‡	66.2 ± 2.7	65.7 ± 2.5	74.0 ± 2.6	67.9 ± 3.8¶	73.5 ± 3.3	70.1 ± 2.0§
Forearm blood flow (ml/100 ml/min)	3.9 ± 0.9	3.7 ± 0.6	4.5 ± 0.7	4.4 ± 0.7	2.5 ± 0.6	3.3 ± 0.5¶	2.6 ± 0.7	2.6 ± 0.6	2.0 ± 0.6	2.7 ± 0.5¶	1.9 ± 0.4	2.1 ± 0.3
Forearm vascular resistance (unit)	20.9 ± 3.4	20.5 ± 2.4	19.6 ± 1.7	18.6 ± 2.3	36.6 ± 8.0	25.1 ± 2.2¶	36.6 ± 10.2	33.0 ± 7.4	45.0 ± 6.1	29.9 ± 5.9¶	48.6 ± 7.1	39.2 ± 6.1§
Left ventricular ejection fraction (%)	44.9 ± 11.0	45.9 ± 7.8	47.0 ± 10.3	47.4 ± 10.6	35.6 ± 8.0	42.6 ± 8.1§	40.2 ± 9.6	40.2 ± 8.4	30.9 ± 11.4	38.4 ± 11.0§	26.6 ± 11.2	28.8 ± 9.3
Exercise duration (min)	8.2 ± 3.3	10.8 ± 3.6¶	7.8 ± 3.0	9.9 ± 3.5¶	7.4 ± 3.4	10.4 ± 3.2¶	7.2 ± 2.8	8.2 ± 3.2†	6.6 ± 2.4	8.3 ± 2.6§	7.0 ± 2.6	7.6 ± 3.6
Maximum load (Mets)	5.0 ± 1.3	6.8 ± 2.4¶	4.7 ± 1.2	6.3 ± 2.3	4.5 ± 1.5	6.6 ± 1.1¶	4.3 ± 1.3	4.8 ± 1.3†	3.9 ± 1.1	4.9 ± 1.1¶	4.1 ± 1.2	4.4 ± 1.5

* Pre = pre-treatment value.
† W = value 2 wk after treatment.
‡ $p < 0.05$ compared with pre-treatment value.
§ $p < 0.01$ compared with pre-treatment value.
¶ $p < 0.001$ compared with pre-treatment value.
There were no significant differences in any pre-treatment values between subgroup P and N in each group.

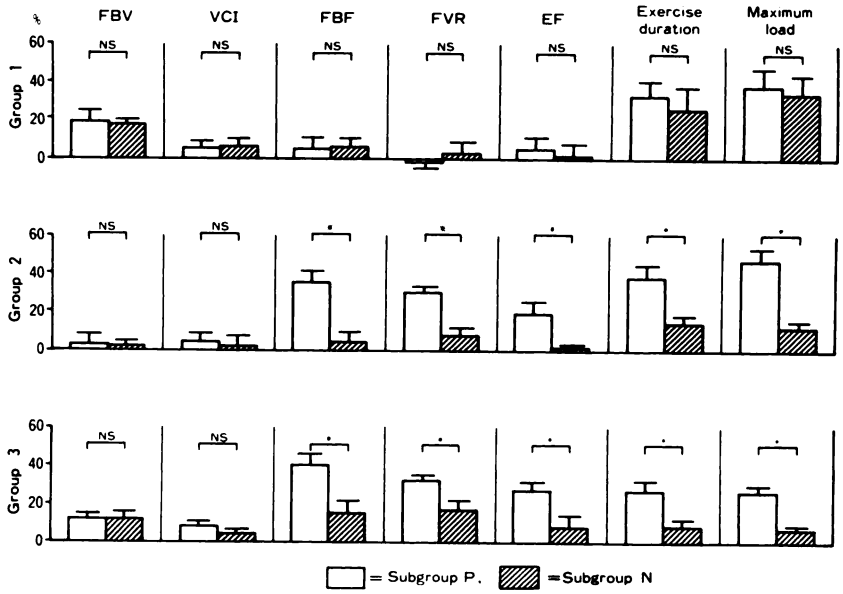

FIGURE 2
Comparisons of percent changes of indexes between subgroup P and N after 2 wk of treatment in Groups 1, 2, and 3. Abbreviations as in text. *:p < 0.05.

filling pressure due to the inadequacy of the effects of the treatment. The administration of isosorbide dinitrate induced vasodilation of CV and, thus, a reduction in venous return, but cardiac output either remained unchanged or even increased, indicating that the drug was also acting on RV. Packer et al. (*10*) also noted that isosorbide dinitrate had vasodilating effects on both vascular systems, but that the effects on RV were concealed in patients with mild heart failure, and suggested the involvement of neurohumoral vasoconstrictor mechanisms in these phenomena.

Nifedipine has vasodilating effects on RV regardless of the severity of impairment of cardiac function, and on CV in patients with mild heart failure. Cantelli et al. (*34*) studied the effects of a single administration of nifedipine, and reported that the treatment decreased pulmonary capillary wedge pressure and total peripheral vascular resistance. Our results suggest that nifedipine has vasodilating effects on CV, though they are significantly weaker ($p < 0.01$) than the effects of isosorbide dinitrate (Fig. 1). The reason for the absence of dilating effect on nifedipine on CV in Group B may be related to the influence of various mechanisms. Marked elevation of adrenergic nervous system is observed in patients with severe heart failure (*35*). Relatively weak venodilating effects of nifedipine seems to be counteracted by the increased venous tone induced by adrenergic nervous system, particularly down regulation of receptors. Nevertheless, Zelis (*36*) stated that the neurohumoral factors play a relatively minor role in the increased venous tone associated with heart failure, and that the decreased venous capacitance in heart failure seems to be related primarily to local factors such as wall stiffness or extravascular tissue pressure. Accordingly, such local factors are also expected to contribute to the absence of the effects of nifedipine on capacitance vessels in severe heart failure.

Calcium channel blocking agents are considered to have negative inotropic effects on myocardium, but EF improved in our study in both Groups A and B. Colucci et al. (*37*) found that nifedipine exerts no inhibitory effects on cardiac function at clinical doses, as was also noted in this study.

Prazosin dilated CV regardless of the severity of

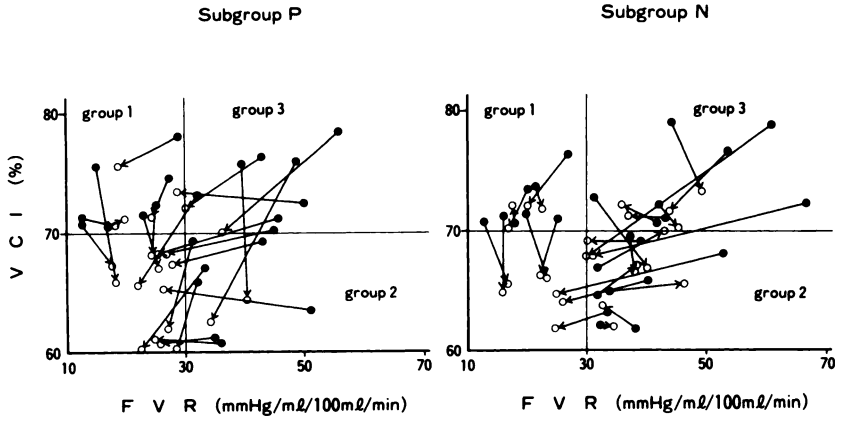

FIGURE 3
Peripheral hemodynamic responses in individual patients of subgroup P and N after 2 wk of treatment. Closed circles (●) indicate the pretreatment values and open circles (○) indicate the value after the treatment. Abbreviations of peripheral hemodynamic indexes are same as in the text.

impairment of cardiac function, and had vasodilating effects also on RV in severe cases, being analogous to the actions of isosorbide dinitrate. The effects of prazosin on CV were significantly weaker ($p < 0.05$) but the effects on RV were significantly greater ($p < 0.05$) than those of isosorbide dinitrate in both groups (Fig. 1).

In Group B, both isosorbide dinitrate and prazosin had comparable effects on the two vascular systems, but prazosin showed the larger percent improvement in EF. While nifedipine had comparable effect on EF with prazosin in Group B, nifedipine did not have vasodilating effect on CV. Venodilatation seems to induce beneficial effects on recovery of patient's symptoms independent of EF. Accordingly, prazosin was selected as optimal drug for the patients with combined elevation of CV and RV in Group B.

Packer (*7,38*) described a new system of classification of vasodilating agents, in which isosorbide dinitrate was considered to induce dose-dependent responses whereas prazosin does not. Nifedipine is also generally considered to show dose-dependent responses. Therefore, increased doses of isosorbide dinitrate or nifedipine may produce different results. Moreover, Magorien et al. (*39*) reported that the effects of prazosin on hepatic blood flow were reversed at doses of 2 mg and 5 mg, and further studies are needed also on this agent. Nevertheless, the doses used in this study are common clinical doses currently given in our country so that evaluation at these doses is considered to be of considerable clinical value.

Based on these differences in the acute effects of the three agents, the following hypothetical criteria for selection of the preferable drug for the treatment of heart failure were formulated: isosorbide dinitrate was considered to be optimal for patients with chronic heart failure showing increased CV tone alone, nifedipine for those showing increased RV tone alone or those showing increased in tone in both vascular systems with EF values of 35% or above, and prazosin for those showing increased tone in both vascular systems with EF of < 35%. If this hypothesis is valid, it is expected to enable selection of the preferable drugs for the treatment of congestive heart failure according to the results of peripheral hemodynamic analysis.

Study 2

To evaluate the validity of the criteria postulated in Study 1, we divided the subjects into three groups according to their peripheral hemodynamic characteristics, and the changes of each variable after 2 wk of treatment were compared between the subjects who were administered the preferable drug and those administered one of the nonpreferable drugs in each group.

In Study 2, it is especially noteworthy that the changes in VCI varied inversely to those in Study 1. The VCI tended to increase immediately after the administration of vasodilators in Study 1. In contrast, they generally decreased after 2 wk of treatment in Study 2. VCI represents the percentage of the volume of blood at rest to the maximum volume of blood contained in the same part of the forearm after venous occlusion. In the acute study, FBV increased rapidly after the drug intervention, however the maximum blood volume did not change significantly. Accordingly, VCI tended to increase. It is thought that the development of peripheral venous wall stiffness, extravascular tissue pressure, and adrenergic nerve stimulation inhibit the expansion of maximum venous dilation during rapid drug intervention. However in the chronic study, vasodilator therapy gradually improved the general cardiovascular conditions, and attenuated the inhibition of venous dilatation. As a result, the increase of maximum blood volume was possibly larger than that of FBV, and VCI tended to decrease in Study 2.

Although isosorbide dinitrate was considered to be optimal for Group 1, the results in the two subgroups showed no significant differences, suggesting that similar effects can be expected by using the other agents. Since many patients in this group had only mild impairment of cardiac function, and since prazosin and nifedipine also have dilating effects on CV as indicated by Study 1, the effects of these agents on these patients were considered to be similar to those of isosorbide dinitrate. The hypothesis, therefore, may not be valid for patients with increased CV tone alone. There is a possibility in this group, however, that indexes of CV showed high values because of inadequate dosage of diuretics. Thus, it is necessary to examine whether or not clinical findings improve by increasing the dosage of diuretics.

In Group 2, improvements in FVR, FBF, EF, and exercise tolerance were significantly greater in subgroup P than in subgroup N. The improvements in exercise capacity appear to be a result of an increase in cardiac output induced by decreased RV tone. Since nifedipine was shown in Study 1 to have the greatest potency in reducing RV tone, the optimal effects of the treatment are expected by the use of this drug in patients with increased RV tone.

Group 3 had the greatest impairment of cardiac function with a mean EF of 29.1%, with 12 of the 16 patients showing EF values of < 35%. Although changes in indexes of CV were not markedly different between the two subgroups, improvements in FVR, FBF, EF, and exercise tolerance were significantly greater in subgroup P. These results suggest that a vasodilating agent with balanced actions on both vascular systems is desirable in patients with a severe condition, supporting the criteria suggested in Study 1. However, the improvement in exercise tolerance observed only in subgroup P, despite the absence of differences in the degree of improvements in CV indexes between the two

subgroups, suggests that a decrease in RV tone more directly contributes to improvements in the exercise capacity in patients with severe heart failure.

Weiner (*40*) stated that maximum oxygen consumption per body weight (VO_2max/kg) is the best index of exercise capacity, but exercise duration, which correlates with VO_2max relatively well, can also be a useful index. However, he cautioned that the results may show ostensible improvements as a result of the effects of repeating practice. This possibility cannot be excluded in our patients in subgroup N of Group 2, who exhibited significant increases in exercise capacity despite no improvements in various indexes of peripheral circulation or EF. However, the degrees of improvements were clearly greater in subgroup P than in subgroup N in Groups 2 and 3. These differences cannot be explained by the effects of practice alone, and appear to be a result of the difference in the effects of the drugs. Vasodilating effects of the preferable drug on resistance vessels are considered to have induced increases in cardiac output and coronary blood flow as well as improvements in myocardial metabolism, contributing to the improvement in exercise tolerance capacity.

The subjects in this study had coronary artery disease or dilated cardiomyopathy. There may be a difference between these two diseases in terms of their hemodynamic responses to the treatment. However, we have an impression from the small number of cases in our study that the responses to the treatment were not different between both types of diseases probably because compensatory mechanism of peripheral vessels is likely to be similar regardless of the causes of cardiac dysfunction (*36*).

The selection of the optimal vasodilator seems to be more important especially in the treatment of patients with severely depressed cardiac function. In our study, 57% of cases with severe heart failure (EF < 35%) were categorized into Group 3, 43% were into Group 2, and no one into Group 1. In the patients with severely depressed cardiac function, increased adrenergic nerve activity, particularly its down regulation of receptors contributes significantly to increased peripheral vascular resistance (*35*). Our data that the most patients with severe heart failure were categorized into either Group 2 or 3 seem to be in agreement with this evidence. From these results, it was thought that the compensatory responses of CV alone are inadequate in the cases of severe heart failure and responses of RV should be necessary for maintaining the central hemodynamic stability (*35*). Peripheral hemodynamic evaluation may play an important role especially in such cases.

Effects of vasodilating agents must be investigated by increasing the doses and using multiple drugs in combinations. Although no side effects or drug tolerance were observed during the short duration of this study, the presence of drug tolerance and the possibility of increasing the doses of digitalis or diuretics must be examined by observation of longer duration.

In this study, since the effects of two different agents were combined in the results of subgroup N, the effects of the three agents could not be compared with each other. Further investigation is needed to establish an effective vasodilating therapy for chronic congestive heart failure. However, our approach may be of value in this area of research because the information of peripheral hemodynamics may be used in establishing criteria for selection of an optimal vasodilator for individual patients with chronic heart failure.

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