INCREASE IN PLASMA NORADRENALINE CONCENTRATION AFTER THE ADMINISTRATION OF PHENTOLAMINE IN THE PATIENTS WITH "LATENT" LEFT-SIDED HEART FAILURE

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We measured increments of peripheral venous pressure induced by dynamic leg exercise (ΔVP) in 10 healthy subjects (Group C) and 70 patients with heart diseases which primarily affect the left-side of the heart. None of the subjects showed apparent symptoms of left- or right-sided heart failure. The patients were divided into 2 groups on the basis of ΔVP , namely, Group N ($\Delta VP < 35 \text{ mmHg}$, $n = 30$, normal reaction) and Group H ($\Delta VP \geq 35 \text{ mmHg}$, $n = 40$, abnormal reaction).

We measured the increments of plasma concentrations of noradrenaline (ΔNA_{PH}) and adrenaline (ΔA_{PH}) with infusion of phentolamine (PH). Parallel studies with nitroglycerin and prazosin supplied strong evidence that ΔNA_{PH} was brought about mainly by the blockade of α_2 -receptors at the sympathetic nerve terminals. Thus, we estimated the degree of sympathetic nerve activity from the central nervous system by opening using PH the negative feed-back loop for noradrenaline (NA) release at the sympathetic nerve terminals, and this degree of sympathetic nerve activity was compared with the degree of ΔVP .

The results obtained were 1) there was a rough overall correlation between ΔVP and ΔNA_{PH} in the subjects of Groups C, N and H, and 2) ΔNA_{PH} was significantly higher in Group H than in Groups C and N.

These results suggest that much reliance can be placed on the measured increment of plasma NA concentration in response to the administration of PH in assessing the degree of enhanced sympathetic nerve activity in the patients with "latent" left-sided heart failure.

IN our laboratory, we have tried to measure the peripheral venous pressure (VP_{40}) together with its increments in response to supine leg exercise (ΔVP), performed by alternate flexion and extension of the hip joint, as one of the

methods of estimating the pumping function of the heart. We have found that the ΔVP of more than 35 mmHg could well reflect a poor function of the left-side of the heart in all cases.¹ In previous studies, we have measured plasma noradrenaline (NA) concentration at rest and the increments of NA during dynamic leg exercise (ΔNA) in patients with cardiac diseases, which primarily affect the left-side of the heart. The physical capacity was that of the former NYHA classes I and II. As a result, we discovered a

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TABLE I SUBJECTS (NYHA CLASS I, II)

	No.	Groups				
		C	N	H	(NG)	(PR)
Normal Control	10	10				
Heart Diseases						
Valvular Heart Disease	23		9	14	(4)	(3)
Ischemic Heart Disease	36		17	19	(4)	(5)
Cardiomyopathy	11		4	7	(2)	(2)
Total	80	10	30	40	10	10
Age (mean $\pm$ SE)		45.4 $\pm$ 6.3	57.6 $\pm$ 1.9	64.5 $\pm$ 1.7	62.5 $\pm$ 3.0	67.0 $\pm$ 3.7

Excluding NYHA class III, IV and peripheral venous pressure (VP_{40}) ≥ 90 mmH₂O

Group C = normal control, Group N: $\Delta VP < 35$ mmH₂O, Group H: $\Delta VP \geq 35$ mmH₂O

PH = phentolamine; PR = prazosin; NG = nitroglycerin

correlation between ΔVP and NA at rest, and between ΔVP and ΔNA . We also found that plasma NA concentration at rest and ΔNA were both higher in patients with a ΔVP of 35 mmH₂O or more than those with a ΔVP of less than 35 mmH₂O.² We suggested that the sympathetic nerve activity was augmented in the patients with "latent" left-sided heart failure having no apparent symptoms of congestive heart failure ($\Delta VP \geq 35$ mmH₂O). After phentolamine (PH, α_1 - and α_2 - blocker) infusion, ΔVP fell to the normal range and the ΔNA increased significantly.³ There was no correlation between ΔVP and ΔNA after PH. From this result, we suggested that the decrease in ΔVP after PH infusion was brought about in 2 ways: (a) PH blocked the postsynaptic α_1 - and α_2 -receptors of the systemic veins whose tone was increased during dynamic exercise, and this action of PH led to dilatation of the systemic veins, (b) PH blocked the presynaptic α_2 -receptors at the sympathetic nerve terminals, and led to an increased release of NA from the sympathetic nerve terminals. The released NA stimulated cardiac β -receptors and caused the cardiac output curve to improve.

Plasma NA concentration at rest in patients with "latent" left-sided heart failure is only slightly higher than in normal subjects, because there is a negative feedback mechanism^{4,5} in which NA released from the sympathetic nerve terminals stimulates the presynaptic α_2 -receptors and this, in turn, inhibits the release of NA, in spite of the increase in sympathetic nerve activity. It was anticipated that plasma NA concentration after PH infusion (ΔNA_{PH}) would be

markedly increased in patients with "latent" left-sided heart failure.

The present study was performed to estimate the degree of sympathetic nerve activity from the central nervous system by using PH to open the negative feedback loop for NA release at the sympathetic nerve terminals in the patients with cardiac disease which affect primarily the left-side of the heart.

SUBJECTS AND METHODS

I) Subjects

A total of 80 subjects comprised 70 patients with heart diseases which primarily affect the left-side of the heart, showing no apparent symptom of congestive heart failure (former NYHA⁶ class I or II) and 10 healthy subjects as a control group (Group C). The patients were divided into two groups on the basis of ΔVP in response to dynamic supine leg exercise.⁷ Namely, those with ΔVP of less than 35 mmH₂O constituted Group N ($n = 30$) and those with ΔVP of 35 mmH₂O or more constituted Group H ($n = 40$).

Underlying disease, and ages of these patients are shown in Table I. When this study was performed, 22 of the 30 patients in Group N and 37 of the 40 patients in Group H had been taking medications, such as digitalis, diuretics, vasodilators etc, which would influence the cardiac pumping function.

II) Methods

1) Measurement of the peripheral venous pres-

Fig. 1. Time schedule of venous blood sampling for the measurement of plasma catecholamine concentrations. For abbreviations, see the glossary of terms.

sure (VP_{40}) and the increments of peripheral venous pressure (ΔVP) due to dynamic supine leg exercise

The method of measurement of ΔVP which we use in our laboratory has been already reported^{7,8}. Using a modified method of Moritz-Tabora, VP_{40} was measured in an antecubital vein at intervals of 30 sec with the patient in a supine position. The zero-pressure reference point was set at a level of 40 mm toward the spine from the anterior chest wall. After measuring VP_{40} , supine leg exercise was performed by alternate flexion and extension of the hip joint 33 times/min, without raising the heel from the mattress, keeping the patient in a supine position. The leg exercise was continued until VP_{40} became stable. In most cases, this appeared about 3 ~ 4 min after starting the exercise. We defined the VP_{40} at this time as VP_{40} during exercise. ΔVP was obtained according to the following formula,

$$\Delta VP (\text{mmHg}) = (VP_{40} \text{ during exercise}) - (VP_{40} \text{ at rest})$$

The reproducibility of the measurement of ΔVP is within $\pm 10 \text{ mmHg}$,⁷ and the normal value of ΔVP is less than 35 mmHg .⁹

2) Measurement of plasma catecholamine (CA) concentrations

A three way needle with wings was slipped into an antecubital vein in the same arm as that used for the measurement of VP_{40} . A physiological saline solution was infused continuously through one of the three ways to secure a patent venous line. Blood samples (about 7 ml each) for the measurement of plasma CA concentrations were obtained through one of the three ways, according to the sampling schedule shown in Fig. 1. ΔVP was obtained, first, 20 min after all the instrumentation of the experiments had been finished. Second, after a further 20 min rest, PH (0.1 mg/kg) was injected intravenously

Fig. 2. Time course change in VP_{40} and plasma catecholamine concentrations in response to exercise or phentolamine infusion in a typical group H case ($\Delta VP \geq 35 \text{ mmHg}$). MRs = mitral regurgitation (dominant) + mitral stenosis, ARs = aortic regurgitation (dominant) + aortic stenosis. For abbreviations, see the glossary of terms.

over 30 sec immediately after obtaining a blood sample as a control (①). Blood samples (② ~ ⑥) were obtained 2, 4, 6, 8 and 10 min after the start of PH infusion. Plasma NA and A concentrations were measured by means of THI method using high performance liquid chromatography (SHIMADU LC-6A, ZORBAX SCX-300, RF-500 LCA).

Plasma NA and A concentrations obtained at the time ① were, by definition, control plasma NA and A concentrations. Increments of plasma NA and A concentrations after PH infusion (ΔNA_{PH} and ΔA_{PH}) were obtained by subtracting the value at the time ① from the highest value among times ② to ⑥. In our laboratory, the reproducibility of the plasma NA and A concentrations 18 min and 20 min after the end of instrumentation is $\pm 7.1\%$ for NA and $\pm 13.0\%$ for A.³

3) Measurements of blood pressure and pulse rate.

Arterial blood pressure and pulse rate were measured throughout the whole course of the experiments at one minute intervals, with an automatic sphygmomanometer (BP 203 YN NIHON COHLIN Co., Ltd.).

4) Drug used

a) Phentolamine (PH)

PH was dissolved in physiological saline and a dose of 0.1 mg/kg was injected into the an-

Fig.3. Time course changes of mean blood pressure and pulse rate before and after phentolamine infusion (mean $\pm$ SE) $\bullet$ = group C (n = 10); $\triangle$ = group N (n = 30); $\circ$ = group H (n = 40).

tecubital vein.

b) Nitroglycerin (NG)

Two tablets of NG (0.3 mg) were administered sublingually, and blood samples were taken according to the same schedule as that for PH.

c) Prazosin (PR)

About 0.04 mg/kg of PR was administered orally and blood samples were obtained 2, 4, 6, 8 and 10 min after blood pressure decreased to the same level as in the case of PH.

5) Statistical analysis

The values are all expressed as mean $\pm$ SE. Statistical analysis between two groups was made using paired or unpaired Student's t-test, and that among three groups was made using one-way analysis of variance, following the multiple comparisons using Scheffe method. A p value of less than 0.05 was considered to be statistically significant.

6) Glossary of terms

A = adrenaline; ΔA_{PH} = increment of plasma adrenaline concentration due to PH; CA = catecholamine; Group H = cardiac patients with ΔVP more than 35 mmH₂O ("latent" left-sided heart failure); MBP = mean blood pressure; Group N = cardiac patients with ΔVP less than 35 mmH₂O; NA = noradrenaline; ΔNA_{NG} = increment of plasma NA concentration due to NG; ΔNA_{PH} = increment of plasma NA concentration due to PH; ΔNA_{PR} = increment of

Fig.4. Time course changes of plasma noradrenaline concentration before and after phentolamine infusion in groups C, N and H.
* = $p < 0.001$ (group H vs group C, group H vs group N). For abbreviations, see the glossary of terms.

plasma NA concentration due to PR; NG = nitroglycerin; PH = phentolamine; PR = prazosin; VP_{40} = peripheral venous pressure; ΔVP = increment of peripheral venous pressure due to dynamic supine leg exercise.

RESULTS

1) Phentolamine (PH)

1) A typical case (in Group H)

Figure 2 shows the time-course changes in peripheral venous pressure and plasma CA concentrations before and after PH infusion in a typical case in Group H. In this case, ΔVP was abnormally high, and plasma NA concentration at rest showed a high value, exceeding the normal upper limit (0.385 ng/ml). After PH infusion, plasma NA concentration increased rapidly, and showed the highest value 6 min after PH infusion. ΔNA_{PH} was markedly high. However, there was no marked change in plasma A concentration.

2) Effect of PH on mean blood pressure (MBP), pulse rate and VP_{40}

Figure 3 shows the time-course changes in MBP and pulse rate before and after PH in the

Fig. 5. Comparison of the increments of plasma noradrenaline concentration (ΔNAPH) due to phentolamine infusion between groups C, N and H. For abbreviations, see the glossary of terms.

three groups. MBP showed a significant fall and pulse rate showed a significant increase after PH infusion in all three groups. We compared maximal percentage changes in the MBP (ΔMBP), because the times at which these parameters changed maximally, differed. These were $-7.3 \pm 2.7\%$, $-13.0 \pm 1.1\%$ and $-15.0 \pm 1.0\%$ in Groups C, N and H, respectively. ΔMBP in Groups N and H were significantly higher than that in Group C. There was no significant difference in maximal percentage changes in pulse rate between the three groups.

The fall in VP_{40} after PH in Groups C, N and H was -7.8 ± 3.5 , -13.0 ± 2.2 and -12.0 ± 3.8 mmHg , respectively. There were no significant differences among the three groups.

3) Time-course changes in plasma CA concentrations

Time-course changes in plasma NA concentration in Groups C, N and H are shown in Fig. 4. Control value (the value before PH infusion) in Group H was significantly higher than in Groups C and N. After PH infusion, plasma NA concentration in Group H increased rapidly and it showed the highest value at the time 4; thereafter, it decreased gradually. Plasma NA concentration in both Groups C and N increased to a lesser degree than in Group H. On the other hand, plasma A concentration increased slightly after PH infusion in all three groups, but the in-

Fig. 6. Relationship between ΔVP and ΔNAPH . Vertical dashed line = ($\Delta\text{VP} = 35$ mmHg), Horizontal dashed line = ($\Delta\text{NAPH} = 0.353$ ng/ml). For abbreviations, see the glossary of terms.

crease was not statistically significant.

4) Increments of plasma CA concentrations (ΔNAPH , ΔAPH) after PH infusion in Groups C, N and H

In the majority of cases, plasma NA concentration showed the highest value 6 min or so after PH infusion, although they varied in each case. Figure 5 shows ΔNAPH in Groups C, N and H. There was no significant difference in ΔNAPH between Groups C (0.178 ± 0.033 ng/ml) and N (0.215 ± 0.017 ng/ml), but ΔNAPH in Group H (0.689 ± 0.049 ng/ml) was significantly (about three times) higher than in Groups C and N. There was no significant difference in ΔAPH between Groups C (0.030 ± 0.008 ng/ml), N (0.023 ± 0.003 ng/ml) and H (0.033 ± 0.004 ng/ml).

5) Relationship between ΔVP and ΔNAPH

As shown in Fig. 6, there was a rough correlation between ΔVP and ΔNAPH . When the normal upper limit of ΔNAPH was defined as 0.353 ng/ml , i.e., the highest value in Group C, then ΔNAPH in Group N was below the normal upper value in all except four cases (82%), and ΔNAPH in Group H showed values higher than

TABLE II $\Delta\text{NA}_{\text{PH}}$ (MEAN $\pm$ SE) IN GROUPS N AND H IN EVERY TEN YEAR CATEGORY, WITH SPECIAL REFERENCE TO SALT RESTRICTION, THE USE OF DIURETICS, AND THE PRESENCE OF RENAL AND LIVER DYSFUNCTION

	Group N		Group H		t-test
	$\Delta\text{NA}_{\text{pH}}$ (ng/ml)	(n)	$\Delta\text{NA}_{\text{pH}}$ (ng/ml)	(n)	
<i>Age</i>					
~ 49	0.188 ± 0.029	(4)	0.465 ± 0.035	(4)	NS
~ 59	0.243 ± 0.026	(11)	0.655 ± 0.063	(9)	< 0.001
~ 69	0.189 ± 0.037	(9)	0.755 ± 0.105	(13)	< 0.001
~ 79	0.248 ± 0.048	(4)	0.724 ± 0.110	(10)	< 0.02
<i>Salt Restriction</i>					
(-)	0.203 ± 0.020	(20)	0.654 ± 0.065	(23)	< 0.001
(+)	0.243 ± 0.029	(10)	0.737 ± 0.075	(17)	< 0.001
<i>Diuretics</i>					
(-)	0.216 ± 0.020	(21)	0.728 ± 0.127	(9)	< 0.001
(+)	0.216 ± 0.032	(9)	0.678 ± 0.053	(31)	< 0.001
<i>Renal Dysfunction*</i>					
(-)	0.219 ± 0.018	(26)	0.692 ± 0.051	(38)	< 0.001
(+)	0.197 ± 0.058	(4)	0.562	(2)	(-)
<i>Liver Dysfunction**</i>					
(-)	0.212 ± 0.017	(29)	0.713 ± 0.053	(36)	< 0.001
(+)	0.339	(1)	0.474 ± 0.041	(4)	(-)

Salt Restriction (+) = 6 ~ 7 g/day

NS = not significant

* = creatinine more than 1.5 mg/dl

** = abnormal value of GOT, GPT, total bilirubin or choline esterase

this value except in two cases (95%).

6) Effects of age, salt restriction, diuretics, renal dysfunction and liver dysfunction on $\Delta\text{NA}_{\text{PH}}$ in Groups N and H.

Table II shows $\Delta\text{NA}_{\text{PH}}$ in Groups N and H in each age decade, with and without salt restriction (6 ~ 7 g/day), diuretics, renal or liver dysfunction. $\Delta\text{NA}_{\text{PH}}$ in group H showed higher values than in Group N regardless of age, salt restriction, diuretics, renal or liver dysfunction.

II) Nitroglycerin (NG)

— Effect of PH vs NG on the plasma NA concentration and MBP in Group H —

The left side of Fig. 7 shows $\Delta\text{NA}_{\text{PH}}$, ΔNANG obtained within three days of PH infusion and ΔMBP in one and the same 10 patients in Group H. Though there was no significant difference in ΔMBP between PH and NG, $\Delta\text{NA}_{\text{PH}}$ (0.539 ± 0.051 ng/ml) was significantly (about three

times) higher than ΔNANG (0.176 ± 0.026 ng/ml).

III) Prazosin (PR)

— Effect of PH vs PR on the plasma NA concentration and MBP in Group H —

The right side of Fig. 7 shows $\Delta\text{NA}_{\text{PH}}$, ΔNAPR obtained within three days of PH infusion and ΔMBP in one and the same 10 patients in Group H. There was no significant difference in ΔMBP with PH and NG. However, $\Delta\text{NA}_{\text{PH}}$ (0.771 ± 0.120 ng/ml) was significantly (about five times) higher than ΔNAPR (0.161 ± 0.035 ng/ml).

DISCUSSION

It is well-known that plasma NA concentration is increased in cardiac patients with apparent symptoms of congestive heart failure (former NYHA class III and IV).¹⁰⁻¹⁶ We reported that

Fig. 7. Comparison between the increments of plasma noradrenalin concentration due to phentolamine (ΔNA_{PH}), nitroglycerine (ΔNA_{NG}) or prazosin (ΔNA_{PR}) and the maximal decrease in mean blood pressure (ΔMBP) in patients of group H. Administrations of PH and NG, PH and PR were performed in one and the same patients. For abbreviations, see the glossary of terms.

both (1) plasma NA concentration at rest and (2) the increment of NA during dynamic leg exercise (ΔNA) were higher in patients with ΔVP of more than 35 mmHg (‘‘latent’’ left-sided heart failure) than in normal subjects and patients with ΔVP of less than 35 mmHg.² This suggests that the tone of the sympathetic nervous system was already increased in the patients with ‘‘latent’’ left-sided heart failure (former NYHA class I and II).² It was suggested that left-sided pumping function had declined and the tonus of the capacitance vessels had increased in patients with an abnormally high value of ΔVP of more than 35 mmHg.

In our laboratory, we tried to measure ΔVP and plasma CA concentrations before and after PH infusion to clarify the mechanism by which ΔVP is augmented in cardiac patients with ‘‘latent’’ left-sided heart failure.³ In the course of this study, we found, that the increment of plasma NA concentration 3 min after PH infusion (immediately before leg exercise) was more marked in patients with ΔVP of more than 35 mmHg (0.303 ± 0.051 ng/ml, $n = 23$) than in those with ΔVP of less than 35 mmHg (0.125 ± 0.021 ng/ml, $n = 18$).

Though it has been reported¹⁷ that plasma NA concentration increased in cardiac patients after PH infusion, as far as we know, there has been no report documenting that the increment

Fig. 8. Hypothesis for the genesis of increased increments of plasma noradrenaline concentration.

The figure shows the sympathetic nervous terminals. $\downarrow$ = the degree of the sympathetic nervous activity, $\square$ = noradrenalin, $\blacksquare$ = the blockade of α_2 -receptors by phentolamine, phentolamine (-) = no pretreatment with phentolamine, phentolamine (+) = with pretreatment with phentolamine.

in plasma NA concentration after PH infusion varies in proportion to the degree of left-sided heart pumping dysfunction. In this study, ΔNA_{PH} was about three times higher in Group H than in Group N (Fig. 5). Plasma NA concentration at rest (0.419 ± 0.024 ng/ml) in Group H was about twice as high as that (0.196 ± 0.011 ng/ml) in Group N (Fig. 4). The difference in ΔNA_{PH} between Groups N and H was greater than that of plasma NA concentration at rest between Groups N and H.

Figure 8 illustrates our hypothetical explanation. As shown in the left-upper part of Fig. 8, suppose that the sympathetic nerve activity is normal as shown for Group C or N. Here, some of the NA released from the sympathetic nerve terminals combines with α_2 -receptors of the sympathetic nerve terminals, thereby inhibiting the release of NA (negative feedback). However, if the pumping function of the left-side of the heart had decreased as in Group H, as shown in the right upper part of Fig. 8, the sympathetic nerve activity would be augmented. As a result, the amount of NA which combines with α_2 -receptors at the sympathetic nerve terminals would increase and the overall release of NA

from the sympathetic nerve terminals would be partly blocked. Therefore, plasma NA concentration at rest in Group H would increase only slightly above the levels of Group C or N, although the sympathetic nerve activity in Group H was augmented. As shown in the right lower part of Fig. 8, it is speculated that α_2 -receptors at the sympathetic nerve terminals are blocked by PH, thereby opening the negative feedback loop and increasing markedly the release NA, especially in the case of Group H.

We compared ΔN_{ANG} with ΔN_{APH} in the same patients with abnormal values of ΔVP , to clarify whether or not the increased release of NA after PH was partly brought about by baroreceptor reflex.¹⁸ As a result, ΔN_{APH} was significantly higher than ΔN_{ANG} (Fig. 7). This result suggested that the major part of the increase in plasma NA concentration after PH was brought about by mechanisms other than the baroreceptor reflex. We do not know the role played by the cardiopulmonary reflex,¹⁹ but we know from our animal experiments that venous return increases, not decreases, after the administration of PH.²⁰ To make sure that ΔN_{APH} was induced by the blockade of α_2 -adrenoceptors at the sympathetic nerve terminals, we measured the increment of NA (ΔN_{APR}) after the oral administration of PR, an α_1 -blocking agent,²¹ in the same patients with abnormal ΔVP , and we compared ΔN_{APR} with ΔN_{APH} . ΔN_{APR} was significantly lower than ΔN_{APH} . Although there remains a problem in that PR was administered orally, while PH was administered intravenously, it may be suggested that the ΔN_{APH} was not brought about by the blocking effect of PH on α_1 -adrenoceptors.

As shown in Table II, age, salt restriction, diuretics, renal dysfunction or hepatic damage seemed hardly to affect the ΔN_{APH} . Thus, ΔN_{APH} was significantly higher in the patients with abnormal ΔVP , in whom the existence of decreased pumping function of the left-side of the heart is probable.

The results in the present study suggest that we can assess the degree of sympathetic nerve activity from the central nervous system by measuring the ΔN_{APH} and this degree closely reflects the degree of impairment of the pumping function of the left-sided heart.

REFERENCES

1. HORIE K, GOTOH K, SUZUKI T, YASUDA Y, FUJIWARA H, OHSUMI Y, YAGI Y, HIRAKAWA

- S: Predictability of left heart dysfunction from right heart performance. —Cardiac index-venous pressure plots and cardiac index-mean pulmonary artery wedge pressure plots at rest and their shift during dynamic exercise— *Jpn Circ J* 53: 219, 1989
2. ISHIMURA K, ITO H, MINATOBUCHI S, SUZUKI S, WATANABE H, MIYAUCHI Y, HIRAKAWA S: Response of peripheral venous pressure and plasma catecholamine concentration to supine leg exercise. —A study in patients with mild congestive heart failure— *Jpn Circ J* 52: 119, 1988
3. SUZUKI S, ITO H, ISHIMURA K, MINATOBUCHI S, WATANABE H, HIRAKAWA S: Effects of phentolamine on response to supine leg exercise of peripheral venous pressure and plasma catecholamine concentration. —A study in patients with mild congestive heart failure— *Jpn Circ J* 51: 1257, 1987
4. LANGER SZ: Presynaptic receptors and their role in the regulation of transmitter release. *Br J Pharmac* 60: 481, 1977
5. HOFFMAN BB, LEFKOWITZ RJ: Alpha-adrenergic receptor subtypes. *N Engl J Med* 302: 1390, 1980
6. RUSK HA, GERTLER MM: Rehabilitation in congestive heart failure. *Circulation* 21: 444, 1960
7. ITO A: Effect of nitroglycerin on peripheral venous pressure at rest and during exercise in patients with heart diseases. *Jpn Circ J* 41: 67, 1977 (in Japanese)
8. KONDO Y: The measurements of venous pressure. *Clinic All-Round* 20: 936, 1971 (in Japanese)
9. HIRAKAWA S, KINOSHITA M, HAYASE S: Noninvasive assesment of the performance of the right heart during dynamic exercise a study of left-sided heart disease. *Jpn Circ J* 40: 35, 1976
10. THOMAS JA, MARKS BH: Plasma norepinephrine in congestive heart failure. *Am J Cardiol* 41: 233, 1978
11. FRANCIS GS, GOLDSMITH SR, ZIESCHE SM, COHN JN: Response of plasma norepinephrine and epinephrine to dynamic exercise in patients with congestive heart failure. *Am J Cardiol* 49: 1152, 1982
12. LEVINE TB, FRANCIS GS, GOLDSMITH SR, SIMON AB, COHN JN: Activity of the sympathetic nervous system and renin angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 49: 1659, 1982
13. FRANCIS GS, GOLDSMITH SR, COHN JN: Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. *Am Heart J* 104: 725, 1982
14. LEHMANN M, KEUL J, DICKHUTH HH: Plasma catecholamines and hemodynamics in patients with heart failure. *Herz* 7: 188, 1982 (in German)
15. VIQUERAT CE, DALY P, SWEDBERG K, EVERS C, CURRAN D, PARMLEY WW, CHATTERJEE K: Endogenous catecholamine level in chronic heart failure. *Am J Med* 78: 455, 1985
16. MINAMI M, YASUDA H, YAMAZAKI N, KOJIMA S, NISHIJIMA H, MATUMURA N,

- TOGASHI H, KOIKE Y, SAITO H: Plasma norepinephrine concentration and plasma dopamine-beta-hydroxylase activity in patients with congestive heart failure. *Circulation* 67: 1324, 1983
17. CREAGER MA, FAXON DP, CUTLER SS, KOHLMANN O, RYAN TJ, GAVRAS H: Contribution of vasopressin to vasoconstriction in patients with congestive heart failure: Comparison with the renin-angiotensin system and the sympathetic nervous system. *J Am Coll Cardiol* 7: 758, 1986
18. ITO H: Adrenoceptor mechanism in the canine systemic capacitance vessels – A study with the measurement of mean circulatory pressure – *J Jpn Coll Angiol* 26: 297, 1986
19. BRANDENBURG RO, GIULIANI ER, MCGOON DC: Reflexes from the heart and lungs. *Cardiology* 170, 1987
20. ITO H, MINATOBUCHI S, HIROSE I, SUZUKI S, WATANABE H, HIRAKAWA S: An investigation from right ventricular output curve and venous return curve. In Hemodynamics in Congestive Heart Failure, ed by WATANABE Y, Suzuken Center, Nagoya, 1987, p 15 (in Japanese)
21. CONSTANTINE JW, GUNNELL D, WEEKS RA: α_1 - and α_2 -vascular adrenoceptors in the dog. *Eur J Pharmacol* 66: 281, 1980