THE EFFECTS OF PHENTOLAMINE AND NITROGLYCERIN ON RIGHT-SIDED HEMODYNAMICS IN CARDIAC PATIENTS CAN BE EXPLAINED BY A SHIFT OF THE SYSTEMIC VENOUS RETURN CURVE AND RIGHT-VENTRICULAR OUTPUT CURVE

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The present study investigated the effects of phentolamine (PH) and nitroglycerin (NG) on the hemodynamics of the right heart in patients with cardiac disease. The patients were divided into a well-functioning left heart group (W group, n=15) and a poorly-functioning left heart group (P group, n=15). Right cardiac hemodynamic parameters and plasma noradrenaline (NA) and adrenaline (A) concentrations were measured before and after administering PH (0.1 mg/kg, i.v.) or NG (0.6 mg, sublingual). In a parallel animal study we obtained a systemic venous return curve by measuring mean circulatory pressure (MCP), mean right atrial pressure (RAP) and cardiac output, before and after administering PH (0.1 mg/kg, i.v.) or NG (12.5 μg/kg, i.v.) to anesthetized open-chest dogs (n=14). We used MCP data (W group: 7.5 mmHg, P group: 10 mmHg) obtained in a separate series of human studies in our laboratory. We constructed the venous return curve by connecting the MCP point on the abscissa with the cardiac index (CI)-RAP plot obtained in the clinical study. We also constructed the right ventricular output curve by connecting the point of -2 mmHg on the abscissa with the CI-RAP plot.

We obtained the following results:
(1) PH shifted the CI-RAP plot to the left and upwards, while NG shifted the CI-RAP plot to the left almost horizontally on the CI-RAP plane, where CI was plotted on ordinate and RAP on abscissa. The length (C PH, C=control point, PH=point after PH) of the shift of CI-RAP plot due to PH was greater in the P group than in W group, while there was no difference in the length (C NG, C=control point, NG=point after NG) of the shift of CI-RAP plot due to NG between P and W groups.
(2) Both PH and NG significantly elevated plasma NA and A concentrations in both the W and P groups. In the P group, PH increased the plasma NA concentration significantly more than did NG, but both drugs increased plasma A concentration to a similar extent.
(3) Both PH and NG significantly decreased the mean pulmonary arterial pres-

Key words:
- Plasma noradrenaline
- Phentolamine
- Nitroglycerin
- Right ventricular output curve
- Systemic venous return curve

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sure with NG doing so significantly more than PH. (4) In anesthetized open-chest dogs, PH 100 μg/kg i.v. rotated the venous return curve clockwise and shifted it to the left, while NG 12.5 μg/kg i.v. shifted the venous return curve parallel to the left. We interpreted the changes in the CI-RAP plot caused by PH and NG in human studies on the basis of venous return curve changes obtained in the dog experiments.

It is suggested that the PH-induced increase in cardiac output is due to (a) stimulation of β-adrenoceptors in the systemic capacitance vessels (a decrease in resistance to venous return) by PH-induced increase in plasma NA level and (b) an improvement in pumping function of the right heart by the stimulation of cardiac β-adrenoceptors by a PH-induced increase in plasma NA level.

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The first vasodilator to be used clinically for the treatment of congestive heart failure was phenolamine (PH), an α-blocking agent1 PH which has both α2-adrenoceptor blocking activity and α1-adrenoceptor blocking activity, has been shown to facilitate the release of noradrenaline (NA) from sympathetic nerve endings in animal experiments.5,6 Increased plasma NA levels are probably responsible for the improvement of congestive heart failure in patients receiving PH, if in fact PH facilitates the release of NA in humans. Our laboratory has reported that injecting 0.1 mg/kg of PH intravenously markedly increased plasma NA concentration in patients with impaired pumping function of the left heart, probably by blocking α2-adrenoceptors at sympathetic nerve endings.7 Judging from these data, PH not only has a vasodilator effect, but also stimulates cardiovascular β-adrenoceptors by increasing NA levels.

In the present study, we measured the changes in hemodynamic parameters and plasma catecholamine concentrations before and after administering PH or nitroglycerin in patients with mild congestive heart failure (NYHA classification I to II). We also evaluated the effects of these drugs on the pattern of the systemic venous return curve in a parallel animal experiment. We interpreted the different hemodynamic effects of these 2 drugs, (1) by constructing human systemic venous return curves which were based upon the changing patterns of systemic venous return curves noted in animal experiments, and (2) by constructing hypothetical right ventricular output curves, and (3) by considering changes in plasma catecholamine concentrations.

SUBJECTS AND METHODS

(I) Clinical Study

1) Subjects

As shown in Table I, 60 patients (NYHA class I to II) with cardiac diseases primarily affecting the left heart were included in the present study. Almost all of the patients (n=53) were taking medications such as cardioactive agents (n=11), diuretics (n=21), and vasodilators (n=50). Chest X-rays revealed cardiomegaly with cardiothoracic ratios of more than 50% in 35 out of 60 patients. All the hypertensive patients had a history of hypertension of more than 5 year duration.

2) Measurements of hemodynamics

A Swan-Ganz catheter was inserted through the right femoral vein with the patient supine. According to the time schedule shown in Fig. 1, we measured mean pulmonary artery wedge pressure (PAW), mean pulmonary arterial pressure (PAP), and mean right atrial pressure (RAP) as well as measuring cardiac output (CO) by the thermodilution method. Heart rate (HR) was calculated from the ECG. Blood pressure was measured in the same arm at 1 min intervals with an automatic sphygmomanometer (BP203, YN, NIHON Colin Co., Ltd). Blood samples for determining plasma catecholamine concentrations were taken through a 19-gauge needle with wings inserted into a contralateral antecubital vein. We defined the time point when all the instrumentation was completed as zero minute. After resting for 20 min, the patient performed alternate flexion and extension dynamic leg exercise in a supine position for about 4 min at a rate of 33 cycles per min without elevating the heel from the

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TABLE I  SUBJECTS (NYHA CLASS I OR II)

<table>
<thead>
<tr>
<th></th>
<th>$W_{PH}$ Group</th>
<th>$P_{PH}$ Group</th>
<th>$W_{NG}$ Group</th>
<th>$P_{NG}$ Group</th>
</tr>
</thead>
</table>
| Valvular Heart Disease  
(mainly Aortic Regurgitation) | 1              | 3              | 3              | 3              |
| Ischemic Heart Disease  
(Old Myocardial Infarction)  
(Angina Pectoris)  
(Hypertensive Heart Failure) | 12(8)          | 12(8)          | 12(6)          | 8(4)           |
| Age (Mean±SE) | 57.5±2.8       | 65.6±1.7       | 59.6±2.5       | 61.0±3.1       |
| Total         | 15             | 15             | 15             | 15             |

$W$ group (well-functioning left heart) = $\Delta CI/\Delta PAW > 0.18 L/min^{-1}M^{-2}mmHg^{-1}$; $P$ group (poorly-functioning left heart) = $\Delta CI/\Delta PAW \leq 0.18 L/min^{-1}M^{-2}mmHg^{-1}$; $PH$ = phenolamine; $NG$ = nitroglycerin; $\Delta CI$ = increments of cardiac index; $\Delta PAW$ = increments of mean pulmonary artery wedge pressure; $W_{PH}$ Group = $W$ group in the presence of $PH$; $P_{PH}$ Group = $P$ group in the presence of $PH$; $W_{NG}$ Group = $W$ group in the presence of $NG$; $P_{NG}$ Group = $P$ Group in the presence of $NG$.

![Fig.1. Time schedule of the study in humans.](image)

Mattress The oxygen consumption, calculated with a spirometer (ss-80 NO.9679, FUKUDA Co., Ltd), was $3.8\pm0.1$ ml/kg/min at rest (mean±SE, n=20) and $7.1\pm0.3$ ml/kg/min during exercise, corresponding to about 2 METS.

3) Separation of the patients into well-functioning and poorly-functioning left heart groups

We measured the increment of cardiac index ($\Delta CI$) and that of mean pulmonary artery wedge pressure ($\Delta PAW$) during exercise, and defined the patient with $\Delta CI/\Delta PAW$ greater than $0.18 L/min^{-1}M^{-2}mmHg^{-1}$ as having a well-functioning left heart ($W$ group, n=30), and the patient with $\Delta CI/\Delta PAW$ less than or equal to $0.18 L/min^{-1}M^{-2}mmHg^{-1}$ as having a poorly-functioning left heart ($P$ group, n=30). Twenty min after the exercise was completed, we administered phenolamine (PH) or nitroglycerin (NG) to patients at random, (a) 0.1 mg/kg of PH was injected intravenously over 30 sec in 15 patients from $W$ group and in 15 from $P$ group ($W_{PH}$ group and $P_{PH}$ group, respectively), or (b) 0.6 mg of NG was administered sublingually to the remaining 15 patients from $W$ group and to the remaining 15 from $P$ group ($W_{NG}$ group and $P_{NG}$ group, respectively). We

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TABLE II HEMODYNAMIC PARAMETERS AND PLASMA CATECHOLAMINE CONCENTRATIONS AT REST

<table>
<thead>
<tr>
<th></th>
<th>PH W_{PH} Group</th>
<th>PH P_{PH} Group</th>
<th>NG W_{NG} Group</th>
<th>NG P_{NG} Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CI (ml/M^2)</td>
<td>3.2 ± 0.1</td>
<td>2.8 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>2.8 ± 0.1</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>7.3 ± 0.7</td>
<td>8.9 ± 0.9</td>
<td>7.9 ± 0.5</td>
<td>10.3 ± 0.9</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>5.2 ± 0.4</td>
<td>5.7 ± 0.6</td>
<td>4.8 ± 0.3</td>
<td>5.7 ± 0.4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>12.7 ± 0.7</td>
<td>15.9 ± 1.4</td>
<td>13.4 ± 0.6</td>
<td>16.7 ± 1.1</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>83.7 ± 1.8</td>
<td>90.7 ± 3.8</td>
<td>85.8 ± 2.2</td>
<td>86.3 ± 1.9</td>
</tr>
<tr>
<td>TPR (dyne-sec-cm^{-5})</td>
<td>1358 ± 62</td>
<td>1717 ± 119</td>
<td>1426 ± 86</td>
<td>1629 ± 91</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>66 ± 3</td>
<td>65 ± 3</td>
<td>65 ± 3</td>
<td>64 ± 2</td>
</tr>
</tbody>
</table>

Plasma Catecholamine Concentrations

<p>| | | | | |</p>
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<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NA (ng/ml)</td>
<td>0.176 ± 0.023</td>
<td>0.338 ± 0.022**</td>
<td>0.177 ± 0.020</td>
<td>0.322 ± 0.060*</td>
</tr>
<tr>
<td>A (ng/ml)</td>
<td>0.036 ± 0.006</td>
<td>0.059 ± 0.009</td>
<td>0.037 ± 0.004</td>
<td>0.053 ± 0.009</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE.

RAP = mean right atrial pressure; PAP = mean pulmonary arterial pressure; MBP = mean blood pressure;
TPR = total peripheral resistance; HR = heart rate; NA = noradrenaline; A = adrenaline; *=p<0.05;
**=p<0.01 (W Group vs P Group).
For other abbreviations, see Table I.

Fig.2. Shift of cardiac index-mean right atrial pressure (RAP) plot with administration
of phentolamine or nitroglycerin.
* = p<0.05; ** = p<0.01; *** = p<0.001; C = control.
For other abbreviations, see Table I.

used sublingual NG because the effect of
sublingual NG on time course change in
blood pressure was very similar to that of an
intravenous injection of PH, and sublingual
NG decreased blood pressure to the same
extent as PH.

4) Determination of plasma noradrena-
line (NA) and adrenaline (A) concentrations

Blood samples were taken at time points 1
to 7 as shown in Fig. 1. Plasma NA and A
concentrations were measured by high per-
formance liquid chromatography (SHIMAZU
LC-6A, ZORBAX SCX-300, RF500LCA) coupled with the trihydroxyindole

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(THI) method. We defined the plasma NA and A concentrations at time point 1 as the plasma NA and A concentrations at rest before exercise (C_{EX}), and those at time point 2 as the control concentrations of plasma NA and A before the administration of drugs. The highest concentrations of plasma NA and A determined between time points 3 and 7 after the administration of PH or NG were defined as the plasma NA and A concentrations with PH (NA_{PH}, A_{PH}) or those with NG (NA_{NG}, A_{NG}). The normal upper limits of plasma NA and A concentrations in our laboratory are 0.385 and 0.104 ng/ml, respectively. The measurements are reproducible.

(II) Animal experiments
We measured mean circulatory pressure (MCP), CO and RAP in open-chest dogs anesthetized with pentobarbital and kept on artificial respiration. We have previously described the details of our method for measuring MCP. CO was plotted on the ordinate and RAP on the abscissa. A simplified systemic venous return curve was constructed by connecting with a straight line the CO-RAP plot and MCP plotted on the abscissa. We investigated the effects of PH or NG on the patterns of systemic venous return curves. CO was considered to be equal to venous return. The doses of PH and NG used were 100 and 12.5 μg/kg i.v., respectively; these were quite similar to those used in the clinical study.

(III) Extrapolation of venous return curve and right ventricular output curve obtained in the dog experiment to clinical data
We estimated a right ventricular output curve by connecting with a straight line a point of −2 mmHg on abscissa and a CO-RAP plot. The MCP data obtained by a radionuclide forearm occlusion plethysmography in a separate series of human studies in our laboratory showed that MCP was about 7.6 mmHg in NYHA class I cardiac patients and about 9.6 mmHg in NYHA class II–III patients. Therefore, we defined the MCP in patients in W and P groups to be about 7.5 and 10 mmHg, respectively. We constructed the right ventricular output curve by drawing a straight line going up-
Fig. 4. Mean blood pressure (MBP) before and after administration of phentolamine (PH) or nitroglycerin (NG).
C = control; \( \Delta \text{MBP} \) = decrements of MBP; \(* = p<0.05; \quad *** = p<0.001\). For other abbreviations, see Table I.

Fig. 5. Total peripheral resistance (TPR) before and after administration of phentolamine (PH) or nitroglycerin (NG).
C = control; \( \Delta \text{TPR} \) = decrements of TPR; \(* = p<0.05; \quad ** = p<0.01; \quad *** = p<0.001\). For other abbreviations, see Table I.
Fig. 6. Plasma noradrenaline (NA) concentration before and after administration of phenolamine (PH) or nitroglycerin (NG).
C = control; CEX = control for exercise; ΔNA = increments of NA; * = p<0.05; ** = p<0.01; *** = p<0.001.
For other abbreviations, see Table I.

Fig. 7. Plasma adrenaline (A) concentration before and after administration of phenolamine (PH) or nitroglycerin (NG).
C = control; CEX = control for exercise; ΔA = increments of A; * = p<0.05; ** = p<0.01.
For other abbreviations, see Table I.
### TABLE III HEMODYNAMIC PARAMETERS BEFORE AND AFTER THE ADMINISTRATION OF PHENTOLAMINE (PH) OR NITROGLYCERIN (NG) IN DOGS

<table>
<thead>
<tr>
<th></th>
<th>MBP (mmHg)</th>
<th>ΔMBP</th>
<th>TPR (dyne·sec·cm⁻¹)</th>
<th>ΔTPR</th>
<th>MCP (mmHg)</th>
<th>CO (ml/min/kg)</th>
<th>RVR (dyne·sec·cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>PH</td>
<td>105 ± 6</td>
<td>75 ± 4 b</td>
<td>5948 ± 247</td>
<td>3897 ± 326 b</td>
<td>-2051 ± 131</td>
<td>9.8 ± 0.4</td>
<td>7.6 ± 0.3 b</td>
</tr>
<tr>
<td>(n=7, 100 µg/kg, i.v.)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NG</td>
<td>87 ± 3</td>
<td>60 ± 3 b</td>
<td>5602 ± 462</td>
<td>4197 ± 452 b</td>
<td>-1404 ± 201</td>
<td>9.1 ± 0.4</td>
<td>8.5 ± 0.5 b</td>
</tr>
<tr>
<td>(n=7, 12.5 µg/kg, i.v.)</td>
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</tbody>
</table>

Values are expressed as mean ± SE.

MBP = mean blood pressure; TPR = total peripheral resistance; MCP = mean circulatory pressure; CO = cardiac output; RVR = resistance to venous return; ΔMBP = decrements of MBP; ΔTPR = decrements of TPR; a = p < 0.05 (PH vs NG); b = p < 0.01 (Before vs After).

IV. Glossary of terms

- Δ = decrease
- A = increase
- Ad = adrenaline
- Na = noradrenaline
- NG = nitroglycerin
- Cx = cardiac output
- PA = peripheral arterial
- RVR = resistance to venous return
- MB = mean blood pressure

(IV) Statistical analysis: All values were expressed as mean ± SE. The Student's t-test was used to estimate significant differences between groups. A p value less than 0.05 was considered to be significant.

(IV) Statistical analysis: All values were expressed as mean ± SE. The Student's t-test was used to estimate significant differences between groups. A p value less than 0.05 was considered to be significant.
RESULTS

[I] Clinical Study

1) Hemodynamics and plasma noradrenaline (NA) and adrenaline (A) concentrations at rest

The hemodynamic parameters and plasma catecholamine concentrations for each group are shown in Table II. There were no significant differences in hemodynamic parameters between the groups. The plasma catecholamine concentrations shown in Table II are the control values obtained just before the administration of drugs. There were no significant differences in plasma NA concentration between the W group in the presence of PH (WPH group) and the W group in the presence of NG (WNG group) or between the P group in the presence of PH (PPH group) and P group in the presence of NG (PNG group). When we compared the plasma NA concentration between the WPH and PPH groups, and between the WNG and PNG groups, the plasma NA concentration in P group was significantly higher than in the W group. There were no differences in plasma A concentration between the groups.

2) Changes in hemodynamic parameters due to phentolamine (PH) and nitroglycerin (NG)

(a) Changes in cardiac index (CI)-mean right atrial pressure (RAP) plot

Figure 2 shows the changes in the CI-RAP plot due to PH and NG in the W and P groups. The ordinate shows CI and the abscissa shows RAP. PH significantly shifted the CI-RAP plot to the left and upwards in both the WPH and PPH groups. In the WPH group RAP was 4.7±0.5 mmHg, and CI was 3.6±0.1/lM² after PH. In the PPH group RAP was 4.7±0.6 mmHg, and CI was 3.4±0.3/lM² after PH. However, there were no significant differences in the decrements of RAP (ΔRAP) or the increments of CI (ΔCI) between the WPH and PPH groups. The length of the shift of CI-RAP plot due to PH was greater in P group ( |ΔPH| = 1.38±0.18, C = control point, PH = point after PH) than in W group ( |ΔPH| = 0.82±0.20). NG significantly shifted the CI-RAP plot to the left almost horizontally. The RAP after NG was 3.7±0.4 mmHg in the WNG group, and 4.3±0.4 mmHg in the PNG group. However, there were no significant differences in RAP between the 2 groups. There was no difference in the length of the shift of CI-RAP plot due to NG between P ( |ΔNG| = 1.48±0.18, C = control, NG = point after NG) and W ( |ΔNG| =
1.19±0.19) groups.
(b) Changes in mean pulmonary arterial pressure (PAP)

As shown in Fig. 3, both PH and NG significantly decreased PAP compared to control values (C) in all groups. There were no significant differences in the amount (ΔPAP) by which PAP decreased between the W_{PH} (−2.3±0.3 mmHg) and P_{PH} (−2.9±0.5 mmHg) groups, or between the W_{NG} (−4.0±0.5 mmHg) and P_{NG} (−4.9±0.6 mmHg) groups. However, when the W_{PH} and W_{NG} groups, and the P_{PH} and P_{NG} groups were compared, ΔPAP was larger in both NG groups than in the PH groups.
(c) Changes in mean blood pressure (MBP)

As shown in Fig. 4, both PH and NG significantly decreased MBP as compared to control values (C) in all groups. However, there were no significant differences in the decrease in MBP (ΔMBP) between the W_{PH} (−9.1±0.9 mmHg) and W_{NG} (−8.0±1.6 mmHg) groups, or between the P_{PH} (−13.4±1.7 mmHg) and P_{NG} (−11.2±1.6 mmHg) groups.
(d) Changes in total peripheral resistance (TPR)

As shown in Fig. 5, both PH and NG significantly reduced TPR compared to the control values (C) in all groups. There were no significant differences in the decrease of TPR (ΔTPR) between the W_{PH} (−317±44) and P_{PH} (−495±72 dyne·sec·cm{−5}) groups, or between the W_{NG} (−99±26) and P_{NG} (−138±46 dyne·sec·cm{−5}) groups. However, ΔTPR in the W_{PH} and P_{PH} groups was significantly greater than that in the W_{NG} and P_{NG} groups, respectively.
(e) Changes in plasma noradrenaline (NA) and adrenaline (A) concentrations

i) Changes in plasma NA and A concentrations due to PH

As shown in Fig. 6 and 7, there were no significant differences in the plasma NA and A concentrations between at rest before exercise (C_{EX}) and the control NA and A concentrations before the administration of PH or NG (C). Plasma NA and A concentrations after PH (N_{APH}, A_{PH}, respectively) increased significantly compared to control values. The increase in plasma NA concentration due to PH (ΔNA_{PH}) was markedly higher in the P group than in the W group. However, there were no significant differences between the 2 groups in the increase of plasma A concentration due to PH (ΔA_{PH}).

ii) Changes in plasma NA and A concentrations due to NG

Plasma NA and A concentrations after NG (N_{ANG}, A_{ANG}, respectively) were signifi-
Fig. 10. Venous return curves due to administration of isoproterenol, prazosin alone or prazosin in the presence of noradrenaline in dogs. Values are expressed as mean ± SE. For other abbreviation, see Fig. 8.

significantly higher as compared to control values (C) in both W and P groups (Figs. 6 and 7). There were no significant differences between the W and P groups in the increase of plasma NA concentration due to NG (ΔNA<sub>NG</sub>) or in the increases of plasma A concentration due to NG (ΔA<sub>NG</sub>).

iii) Comparisons between the effects of PH and NG on the plasma NA and A concentrations

In group P, NA<sub>PH</sub> and ΔNA<sub>PH</sub> were significantly higher than NA<sub>NG</sub> and ΔNA<sub>NG</sub> respectively (Figs. 6 and 7). However, there were no significant differences between NA<sub>NG</sub> and NA<sub>PH</sub> in W group, or between A<sub>NG</sub> and A<sub>PH</sub> in either group (Figs. 6 and 7).

[II] Effect of PH or NG on hemodynamics in dogs

i) Effect on MBP and TPR

Both PH and NG reduced MBP and TPR significantly. There was no significant difference between PH and NG in the decrease in MBP (ΔMBP), but the decrease in TPR (ΔTPR) was significantly greater after PH than after NG (Table III).

ii) Effect on the systemic venous return curve

As shown in Fig. 8, PH shifted the systemic venous return curve to the left on abscissa and rotated it clockwise. NG shifted the systemic venous return curve to the left almost horizontally.

[III] The changes in the CI-RAP plot due to PH or NG in P group can be explained by a shift of systemic venous return curve and right ventricular output curve

As shown in Fig. 9, we extrapolated the patterns of the systemic venous return curve changes due to PH and NG that have been seen in the dog experiments to human study with PH and NG in P group.

The systemic venous return curves and right ventricular output curves in P group were depicted as shown in Fig. 9. The estimated right ventricular output curve of the P<sub>PH</sub> group soared higher than that of the P<sub>NG</sub> group.

DISCUSSION

Phentolamine (PH) has an α<sub>2</sub>-adrenoceptor blocking effect as well as an α<sub>1</sub>-adrenoceptor blocking effect. It is well known that PH accelerates the release of noradrenaline (NA) from sympathetic nerve endings in animal studies via the blockade of presynaptic α<sub>2</sub>-adrenoceptors. In a human study, our laboratory showed that the plasma NA level was elevated after the intravenous administration of PH (0.1 mg/kg) in proportion to the degree of severity of
previous NYHA classification in patients with left-sided heart diseases. According to the data in our laboratory, where plasma NA concentrations were measured before and after the administration of nitroglycerin (NG) or prazosin in such a dose that mean blood pressure fell to the same extent as in PH injection in cardiac patients, PH increased plasma NA concentration to a far greater extent than either NG or prazosin. This suggested that the increase in plasma NA concentration due to PH was mainly induced by the blockade of presynaptic $\alpha_{2}$-adrenoceptors at sympathetic nerve endings atop of the baroreflex or the blockade of $\alpha_{1}$-adrenoceptors at sympathetic nerve endings. These data suggest that PH vasodilator therapy is effective not only because it dilates peripheral vessels, but also because increased NA due to PH favorably affects the cardiovascular system. In the present study, the increase in plasma NA level was markedly higher after PH than after NG (Fig. 6).

PH and NG had different effects on the hemodynamics of the right heart. That is to say, PH increased cardiac output (CO) and decreased mean right atrial pressure (RAP). While NG decreased RAP, it did not change CO (Fig. 2). In the past, such differences in effects of the two drugs were explained by stating that PH increased CO by dilating the systemic resistance vessels, while NG decreased RAP mainly by dilating systemic capacitance vessels. Indeed, the decrease in total peripheral resistance ($\Delta$TPR) due to PH was larger than that due to NG in the present study (Fig. 5). However, in an attempt to analyse the mechanism of an increased CO by PH, we used the concept of venous return curves and the right ventricular output curves. It is virtually impossible to measure the mean circulatory pressure (MCP) directly in humans. Therefore, we used the changing pattern of the venous return curves obtained in the dog experiment. According to a separate study in our laboratory where we drew venous return curves in humans by calculating the systemic mean pressure that was obtained from radionuclide forearm occlusion plethysmography, NG shifted the venous return curve to the left horizontally as in animal studies. So it may be that the change in pattern of the venous return curve caused by PH in humans would be similar to that seen in the dog experiments. When we interpret the hemodynamic effect of PH or NG in extrapolation from the changes in systemic venous return curves due to PH or NG in dogs (Fig. 8), and from the estimated changes in right ventricular output curve and the changes in plasma NA level due to two drugs, it is suggested that PH may increase CO via mechanisms besides those of simply blocking postsynaptic $\alpha_{1}$-adrenoceptors in the systemic resistance vessels and dilating the systemic resistance vessels.

Fig. 10 shows the effects on dog's venous return curves of isoproterenol (1 $\mu$g/kg), a $\beta$-stimulant, and of prazosin (150 $\mu$g/kg), an $\alpha_{1}$-blocker, and of prazosin (150 $\mu$g/kg) during treatment with a continuous intravenous infusion of NA. Isoproterenol and prazosin rotated the systemic venous return curves clockwise indicating a decrease in resistance to venous return (RVR); isoproterenol decreased RVR by $-32.9\pm5.0\%$ and prazosin decreased RVR by $-19.4\pm4.1\%$. These results suggest that dilution of systemic resistance vessels and the resistance element of the systemic capacitance vessels reduce RVR. However, when prazosin was administered under the conditions that NA was infused continuously, the systemic venous return curve rotated clockwise more and RVR decreased more significantly ($p<0.05$); the percentage decrease in RVR was $-34.5\pm5.2\%$. These results suggest that the decrease in RVR was enhanced to a greater extent due to the $\beta$-adrenoceptor stimulating effect of NA on the systemic capacitance vessels during pretreatment with an $\alpha$-adrenoceptor antagonist. Judging from the fact that PH markedly increased plasma NA levels (Fig. 6), PH may have decreased RVR by stimulating $\beta$-adrenoceptors in the systemic capacitance vessels in addition to blocking $\alpha$-adrenoceptors in the resistance vessels. On the other hand, NG hardly affected RVR probably because NG did not increase the plasma NA level as much as PH.

Both PH and NG seemed to improve estimated right ventricular output curves, PH shifting the curve higher than NG. Both PH and NG decreased the mean pulmonary arterial pressure (PAP), a measure of afterload to the right ventricle. The decrease in PAP
(ΔPAP) was larger after NG than after PH (Fig. 3), suggesting that the improvement of the right ventricular output curve was not due simply to the decrease in afterload to the right ventricle. The increased plasma NA due to PH, by stimulating cardiac β-adrenoceptors, may play a major role in improving right ventricular output curve.

The length of the shift of CI-RAP plot which represents the shift of the right ventricular output curve was greater in the P group in the presence of PH (PPH group) than in the W group in the presence of PH (WPH group), while there was no difference in the length of the shift of CI-RAP plot due to NG between the P group in the presence of NG (PNG group) and the W group in the presence of NG (WNG group). These differences between the P and W groups appear to be reflected by the fact that the increase in plasma NA level due to PH was greater in the P group than in the W group, while there was no difference in the increase in plasma NA level due to NG between the P and W groups.

We suggest that PH increases plasma NA concentration, therefore, it may increase CO by inhibiting α-adrenoceptors and stimulating β-adrenoceptors in the systemic capacitance vessels atop of decreasing TPR by α-blockade, and by stimulating cardiac β-adrenoceptors thus improving cardiac pump function, while NG improves cardiac pump function mainly by reducing PAP, a measure of afterload to the right ventricle.

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