Hemodynamic Effects of Nitroprusside on Cardiovascular System

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The effects of nitroprusside (NP) on hemodynamics, especially on venous flow velocity of the inferior vena cava (IVC) were evaluated in 20 remote myocardial infarction patients. NP was given beginning at 10 μg/min, with subsequent increments of 10 μg/min every 5 minutes until the systolic blood pressure was reduced to about 30 mmHg. Pressure was measured by a catheter-tip micromanometer. Flow velocity of IVC was measured by a catheter-tip flow velocity probe.

NP significantly decreased left ventricular systolic pressure, left ventricular end-diastolic pressure, mean aortic pressure, right ventricular systolic pressure, right ventricular end-diastolic pressure, mean pulmonary arterial pressure, mean pulmonary capillary wedge pressure, systemic vascular resistance index (SVRI) and left ventricular volume. Cardiac index (CI) was unchanged and stroke volume index was decreased. IVC pressure was unchanged, while right atrial (RA) pressure decreased. Subsequently, the pressure difference between IVC and RA increased significantly. The amplitude of IVC flow velocity decreased significantly.

Twenty patients were classified into two groups according to whether or not the CI increased by NP. CI increased in 9 patients (group I) and decreased in 11 patients (group D). Compared to group D, control CI and the slope of end-systolic pressure-volume relation were less and the difference between IVC pressure and RA pressure was greater in group I. The patients with higher control SVRI had greater increase in CI during NP. In our study, the greater the depression of cardiac performance and the higher the SVRI, the greater the improvement of left ventricular pumping function during NP.

VASODILATOR therapy has been documented to be useful in treatment of congestive heart failure. It reduces peripheral resistance and increases cardiac output. In the normal subjects, on the other hand, afterload reduction by vasodilators may rather decrease cardiac output. Central and peripheral blood volume seems to significantly contribute to the effectiveness of the vasodilator therapy. Despite many excellent reports on the clinical usefulness of this therapy, the mechanism of the regulation of the circulating blood volume in the vascular system by afterload reduction is not clearly understood yet.

Sodium nitroprusside is one of the most important vasodilator agents, and its cardiac effect has been amply investigated. However, there have been a few studies concerning the effects of sodium nitroprusside on the peripheral circulation, especially little is known.

Key Words:
Nitroprusside
Vasodilator therapy
Inferior vena cava flow velocity
Inferior vena cava pressure
Fig.1. Slope of end-systolic pressure-volume relation was yielded by connecting the end-systolic pressure-volume point at a control state and it during nitroprusside infusion with a straight line. It was indicated by the dashed lines in this figure.

regarding its effect on venous system. The purpose of this study is to investigate the effect of sodium nitroprusside on the heart and the venous system in patients with or without congestive heart failure who had remote myocardial infarction.

METHODS

Patients population

The study population was a group of 20 patients, 19 males and one female, 34 to 68 years in age (mean 56 years). They had documented myocardial infarction with or without congestive heart failure. One patient was taking procaine amide for frequent ventricular premature beats and another patient was receiving β adrenergic blocking agent (Acebutolol HCl) for frequent anginal pain. In the other 18 patients, cardiac medications were discontinued for at least 3 days before the study.

Catheterization and measurements

Routine right and left heart catheterizations were performed by using a 7F Swan Ganz catheter which was inserted through the right femoral vein and by using a Millar’s catheter-tip micromanometer through the right brachial artery. Cardiac output was determined using the thermodilution technique (Edwards model 9500 computer). Biplane left ventricular cineangiograms (30° right and 60° left anterior oblique projections) were obtained at 60 frames/sec with a 35 mm Arritechno cine camera mounted on a 25 cm image intensifier (Siemens Cardioskop U). The ventricle was opacified with 40 ml of Urografin-76 (Schering) injected at a rate of 13 ml/sec through a Millar’s catheter-tip micromanometer (Model PC-484 A, pigtail). Left ventricular and aortic pressures were obtained utilizing this angiographic high-fidelity micromanometer catheter. The transducer was calibrated electronically against mercury at the beginning of each study. The zero shift during the procedure was adjusted by comparison with the pressure obtained simultaneously from the fluid filled catheter connected to the Statham P23 ID pressure transducer.

Blood flow velocity in the inferior vena cava was measured by a catheter-tip flow velocity probe (Millar, model VPC-663A) connecting to a Narcomatic electromagnetic flowmeter (Model RT 500). This probe has an electromagnetic flow velocity sensor mounted 3 cm apart from the catheter-tip and a high-fidelity micromanometer mounted at the tip. The flow velocity sensor was placed at the level of 2 vertebrae below the diaphragm. The hemodynamic parameters were recorded under a normal respiration. The zero flow velocity level was determined electronically as described in the manual and also by placing the probe at the site close to the incision of the brachial vein where the velocity is zero. The calibration of the blood flow velocity signal in cm/sec was made by using the flow velocity calibration unit (M.E.Commercial Corp.).

Pressures, velocity of venous flow and electrocardiogram were recorded on an Electronics for Medicine VR 12 recorder at a paper speed of 150 mm/sec. Additionally, the analog data were stored in the Sony data recorder during the study to be replayed later.

Procedure

Sodium nitroprusside (NP) of 10 mg was dissolved in 5% glucose solution of 500 ml. Fifteen minutes after the control hemodynamic measurements and left ventricular cineangiography, intravenous NP infusion was started. The initial dosage was 10 µg/min, with subsequent increments of 10 µg/min every 5 minutes until the systemic blood pressure was reduced to about 30 mmHg. When the blood pressure dropped below 90 or 100 mmHg, the increment
### TABLE I HEMODYNAMIC EFFECTS OF NITROPRUSSIDE

<table>
<thead>
<tr>
<th></th>
<th>LVSP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>mAOP (mmHg)</th>
<th>RVSP (mmHg)</th>
<th>RVEDP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>mPCW (mmHg)</th>
<th>mRAP (mmHg)</th>
<th>mIVCP (mmHg)</th>
<th>mIVCP-mRAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>136 ± 4</td>
<td>14.9 ± 1.5</td>
<td>105 ± 3</td>
<td>23.6 ± 1.2</td>
<td>4.5 ± 0.4</td>
<td>13.0 ± 0.7</td>
<td>7.1 ± 0.8</td>
<td>2.8 ± 0.3</td>
<td>5.8 ± 0.5</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>NP infusion</td>
<td>113 ± 3</td>
<td>8.1 ± 0.8</td>
<td>92 ± 3</td>
<td>21.4 ± 0.7</td>
<td>3.6 ± 0.3</td>
<td>10.8 ± 0.5</td>
<td>5.0 ± 0.5</td>
<td>1.9 ± 0.2</td>
<td>6.0 ± 0.5</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>p values</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>NS</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<table>
<thead>
<tr>
<th></th>
<th>CI (l/min m²)</th>
<th>SI (ml/m²)</th>
<th>HR (bts/min)</th>
<th>EDV (ml)</th>
<th>ESV (ml)</th>
<th>EF (%)</th>
<th>peak + dp/dt (mmHg/sec)</th>
<th>peak – dp/dt (mmHg/sec)</th>
<th>SVRI (dynes sec cm⁻² m²)</th>
<th>PARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>2.43 ± 0.1</td>
<td>35.9 ± 1.4</td>
<td>68.1 ± 1.9</td>
<td>151 ± 9</td>
<td>94 ± 10</td>
<td>40 ± 3</td>
<td>1378 ± 45</td>
<td>1452 ± 82</td>
<td>3467 ± 192</td>
<td>132 ± 8</td>
</tr>
<tr>
<td>NP infusion</td>
<td>2.41 ± 0.1</td>
<td>32.7 ± 1.1</td>
<td>74.8 ± 2.5</td>
<td>140 ± 9</td>
<td>83 ± 10</td>
<td>44 ± 3</td>
<td>1486 ± 68</td>
<td>1348 ± 78</td>
<td>3039 ± 129</td>
<td>123 ± 8</td>
</tr>
<tr>
<td>p values</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.02</td>
<td>&lt; 0.02</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are given as mean and standard error of the mean (M ± SEM).

**Abbreviations:** NP = nitroprusside; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; mAOP = mean aortic pressure; RVSP = right ventricular systolic pressure; RVEDP = right ventricular end-diastolic pressure; mPAP = mean pulmonary arterial pressure; mPCW = mean pulmonary capillary wedge pressure; mRA = mean right atrial pressure; mIVCP = mean inferior vena caval pressure; mIVCP-mRAP = the difference between mIVCP and mRAP; CI = cardiac index; SI = stroke volume index; HR = heart rate; EDV = left ventricular end diastolic volume; ESV = left ventricular end systolic volume; EF = ejection fraction; peak + dp/dt = left ventricular peak positive dp/dt; peak – dp/dt = left ventricular peak negative dp/dt; SVRI = systemic vascular resistance index; PARI = pulmonary arteriolar resistance index.

### TABLE II COMPARISON OF THE TWO GROUPS CLASSIFIED

<table>
<thead>
<tr>
<th></th>
<th>control LVSP (mmHg)</th>
<th>NP LVSP</th>
<th>control LVEDP (mmHg)</th>
<th>NP LVEDP</th>
<th>control EDV (ml)</th>
<th>NP EDV</th>
<th>control ESV (ml)</th>
<th>NP ESV</th>
<th>control HR (bts/min)</th>
<th>NP HR</th>
<th>slope (mmHg m²/ml)</th>
</tr>
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<tbody>
<tr>
<td>group I</td>
<td>138 ± 6</td>
<td>114 ± 6</td>
<td>14.9 ± 1.8</td>
<td>8.0 ± 0.8</td>
<td>153 ± 12</td>
<td>143 ± 14</td>
<td>98 ± 14</td>
<td>87 ± 14</td>
<td>65 ± 3</td>
<td>71 ± 4</td>
<td>1.73 ± 0.22</td>
</tr>
<tr>
<td>group D</td>
<td>135 ± 6</td>
<td>112 ± 4</td>
<td>14.9 ± 2.4</td>
<td>8.2 ± 1.2</td>
<td>154 ± 15</td>
<td>141 ± 16</td>
<td>94 ± 15</td>
<td>84 ± 16</td>
<td>70 ± 2</td>
<td>78 ± 3</td>
<td>3.93 ± 0.84</td>
</tr>
<tr>
<td>p values</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>control CI (l/min m²)</th>
<th>NP CI</th>
<th>control SVRI (dynes sec cm⁻² m²)</th>
<th>NP SVRI</th>
<th>control mIVCP (mmHg)</th>
<th>NP mIVCP</th>
<th>control mRAP (mmHg)</th>
<th>NP mRAP</th>
<th>control mIVCP-mRAP (mmHg)</th>
<th>NP mIVCP-mRAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>group I</td>
<td>2.17 ± 0.16</td>
<td>2.41 ± 0.13</td>
<td>3866 ± 338</td>
<td>2976 ± 210</td>
<td>6.5 ± 0.7</td>
<td>6.3 ± 0.8</td>
<td>2.6 ± 0.4</td>
<td>1.8 ± 0.4</td>
<td>3.9 ± 0.6</td>
<td>4.5 ± 0.5</td>
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<tr>
<td>group D</td>
<td>2.64 ± 0.09</td>
<td>2.42 ± 0.11</td>
<td>3140 ± 170</td>
<td>3091 ± 167</td>
<td>5.1 ± 0.6</td>
<td>5.7 ± 0.7</td>
<td>2.8 ± 0.4</td>
<td>1.8 ± 0.3</td>
<td>2.3 ± 0.4</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td>p values</td>
<td>&lt; 0.02</td>
<td>NS</td>
<td>NS (&lt; 0.1)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are given as M ± SEM.

**Abbreviations:** NP = nitroprusside; group I = the group of increased cardiac index by NP; group D = the group of decreased cardiac index by NP; slope = the slope of end-systolic pressure-volume relation.
of dosage was withheld for maintaining the systolic perfusion pressure to be within the safe limit. The mean rate of NP administration was 30.5 μg/min (range 20 ~ 50 μg/min). Upon reaching the desired blood pressure, the infusion was maintained at a constant rate, and the hemo-

dynamic measurements and left ventricular cine-
angiography were repeated. After cine ventricu-
lography, NP infusion was discontinued and coronary angiography was performed by the Sones method.

Calculations and statistical analysis

Left ventricular volume was calculated by the area-length method. Derived hemodynamic parameters were calculated as follows: Ejection fraction (EF) = (end-diastolic volume (EDV) - end-systolic volume (ESV))/EDV x 100(%); Stroke volume index (SI) = stroke volume/body surface area (BSA) (ml/m²); Cardiac index (CI) = cardiac output/BSA (l/min m²); Systemic vascular resistance index (SVRI) = (mean aortic pressure - mean right atrial pressure)/CI x 80 (dynes·sec·cm⁻⁵ m²); Pulmonary arteriolar resistance index (PARI) = (mean pulmonary arterial pressure - mean capillary wedge pressure)/CI x 80 (dynes·sec·cm⁻⁵ m²); Slope of end-systolic pressure-volume relation = (end-
systolic pressure before NP - end-systolic pres-
sure during NP)/(ESV before NP - ESV during
NP) x BSA (mmHg m²/ml) (Fig. 1)

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Fig. 2. Relationship between control systemic vascular resistance index (control SVRI) and the change of systemic vascular resistance index from the control (ΔSVRI).

Fig. 3. Effects of nitroprusside on mean inferior vena caval pressure (IVC pressure), mean right atrial pressure (RA pressure) and the difference between IVC pressure and RA pressure (IVC-RA pressure).

Abbreviations: C = control, N = during nitroprusside, ♦ = M ± SEM.

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Fig. 4. A representative example of the effect of nitroprusside on left ventricular pressure (LV pressure), inferior vena caval pressure (IVC pressure) and inferior vena caval flow velocity (IVC flow velocity). (playback from magnetic tape) The arrow indicates the amplitude of flow velocity. ECG = electrocardiogram.

Statistical analysis was done using the paired t-test, the unpaired t-test and the linear regression equation. A p value less than 0.05 was considered significant.

RESULTS

Hemodynamic data are shown in Table I. NP significantly decreased left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), mean aortic pressure (mAOP), right ventricular systolic pressure (RVSP), right ventricular end-diastolic pressure (RVEDP), mean pulmonary arterial pressure (mPAP) and mean pulmonary capillary wedge pressure (mPCW). CI was unchanged and SI decreased significantly. EDV and ESV decreased significantly. EF increased significantly. SVRI decreased, while PARI was unchanged.

Figure 2 shows the relationship between the control SVRI (before NP) and the change of SVRI from the control. The patients with a higher SVRI before NP had a greater reduction in SVRI during NP (r = -0.742, p < 0.001).

During NP, inferior vena caval pressure (IVC pressure) was unchanged (5.8 ± 0.5 to 6.0 ± 0.5 mmHg, NS), while right atrial pressure (RA pressure) decreased significantly (2.8 ± 0.3 to 1.9 ± 0.2 mmHg, p < 0.001). Subsequently IVC pres-
Fig. 6. Comparison of the two groups about control cardiac index (control CI), slope of end-systolic pressure-volume relation (slope of end-syst. P-V relation) and the difference of control inferior vena caval pressure and right atrial pressure (control IVC-RA pressure).
Abbreviations: I = group I, D = group D, * = M ± SEM.

Fig. 7. Relationship between control systemic vascular resistance index (control SVRI) and the change of cardiac index from the control by nitroprusside (ΔCI).

The pressure minus RA pressure increased significantly (3.0 ± 0.4 to 4.2 ± 0.4 mmHg, p < 0.01) (Fig. 3).

A representative example of the effect of NP on hemodynamic parameters is illustrated in Fig. 4. In the control state (before NP), LVSP was 111 mmHg and LVEDP was 31 mmHg. The flow velocity curve in the inferior vena cava (IVC) in each cardiac cycle exhibited a pulsation with a maximal amplitude of 19 cm/sec which is the difference between the peak and the minimal velocity, as indicated by the arrow. With NP infusion, however, the maximal amplitude decreased to 9 cm/sec although mean flow velocity of the IVC increased from 8.7 cm/sec to 13 cm/sec. LVSP and LVEDP decreased to 99 mmHg and 14 mmHg, and SI and CI also decreased from 34 to 31 ml/min/m² and from 2.27 to 2.03 l/min m², respectively. Heart rate decreased from 67 to 65 beats/min. The amplitude of inferior vena cava flow velocity before and during NP in 13 cases is summarized in Fig. 5. It decreased significantly with NP (15 ± 1.7 to 9 ± 1.2 cm/sec, p < 0.001).

Twenty patients were classified into two groups according to whether or not the CI increased by NP. CI increased in 9 patients (group I) and decreased in 11 patients (group D). Table II shows the comparisons of the two groups classified. Compared to the group D, control CI (2.17 ± 0.16 l/min m² in group I and 2.64 ± 0.09 l/min m² in group D, p < 0.02) and the slope of end-systolic pressure-volume relation (1.73 ± 0.22 mmHg m²/ml in group I and 3.93 ± 0.84 mmHg m²/ml in group D, p < 0.02) were less and the control pressure difference between IVC and RA (3.9 ± 0.6 mmHg in group I and 2.3 ± 0.4 mmHg in group D, p < 0.05) was greater in group I (Fig. 6).

Figure 7 shows the relationship between the control SVRI and the change of CI by NP. The patients with higher control SVRI had greater increase in CI during NP (r = 0.555, p < 0.02).
DISCUSSION

Vasodilators now have an important role in the therapy of acute and chronic congestive heart failure. Sodium nitroprusside (NP) is one of the most important vasodilating drugs, and has a balanced effect on both the precapillary resistance bed and the post capillary capacitance bed. In the present study, NP resulted in declines in aortic pressure, systemic vascular resistance and left ventricular size. These results agree with the previous reports on hemodynamic effects of NP. There is ample evidence that NP for failing heart improved the cardiac output and cardiac filling pressure, while NP caused a reduction of cardiac output in patients without heart failure. Chatterjee et al. and Millar et al. observed that cardiac output increased with NP in patients with marked elevation of left ventricular end-diastolic pressure (LVEDP). In an experimental study of dogs using a right-heart bypass preparation, Pouleur et al. observed no significant changes in the venous return curves or mean systemic pressure, indicating that the amount of blood shifted from the central circulation to the systemic circulation was roughly equal to increase in systemic venous capacitance produced by NP after the production of acute left ventricular failure. In this setting, cardiac output increased during NP. These reports revealed the importance of preload for increase in cardiac output by NP. In the present study, LVEDP before NP was not significantly different between the group I and the group D. CI before NP and the slope of end-systolic pressure-volume relation in group I were less than those in group D. The group I had a tendency of high SVRI before NP, and the reduction in SVRI by NP was considerably greater in group I than in group D. Therefore, in our study, the greater the depression of cardiac performance and the higher the SVRI, the greater the improvement of left ventricular pumping function during NP. It has been postulated that afterload mismatch exists in the steady state of normal systolic pressure in patients with myocardial failure. Increased cardiac output during NP could be explained by reduced aortic impedance or afterload so that the wall stress is lowered during ejection and the preload reserve is restored, thereby allowing a larger cardiac output. The present result revealed additional evidence that pressure gradient between inferior vena cava (IVC) and right atrium (RA) contributes significantly to increase in cardiac output with NP. The greater the pressure gradient the larger the increment in cardiac output. Although the mechanism is not clear at present, this might be one of the regulatory mechanisms to facilitate the venous return in the failing heart.

In normal subjects, the flow pattern in IVC becomes pulsatile as the flow approaches the RA, the pulsation which is considered to be generated by events occurring within the heart. Retrograde transmission of pressure pulsations from RA produces a double peaked flow pulsation in the IVC during each cardiac cycle (Fig. 4). The first, largest peak occurs in the early phase of ventricular systole during which the atroventricular junction pulled toward the apex of the heart and atrial pressure falls. During diastole when tricuspid valve opens and atrial pressure falls again, the second peak occurs. Flow approaches zero at the end of diastole and sometimes reverses direction briefly at the time of atrial contraction. In the present study, the velocity of blood flow through the IVC was measured at near the level of the renal veins. The patterns of flow were similar to those previously reported, although the maximal amplitude of flow velocity curve in the control state varied from case to case (Fig. 5). The severity of heart failure or the position of the flow velocity catheter placed at the level of the renal veins might produce these variable amplitudes of the flow velocity.

During NP, maximal amplitude of the flow velocity curve in the IVC decreased significantly, showing rather a plateau curve (Fig. 4). There are several possible explanations for this finding. First, the IVC is a collapsible vessel surrounded by two extravascular chambers (abdominal and thoracic chambers) separated by the diaphragm. Gardner et al. angiographically observed the localized collapse in the IVC near the level of the diaphragm. Wexler et al. postulated that the reduction of oscillation of flow velocity during deep abdominal breathing or Müller maneuver was consistent with the formation of a partial collapse in the IVC at the level of diaphragm, and the patterns of flow velocity beyond such a constriction was not influenced by events within the heart. During NP, mean pressure in the IVC was unchanged, while mean RA pressure was decreased. Therefore, the pressure gradient between IVC and RA was increased (Fig. 3). In addition, maximal amplitude of the flow velocity curve in the IVC decreased.
significantly at that time (Fig. 4). These findings suggest that the IVC may partially collapse at near the level of diaphragm during NP. If so, the flow velocity pattern in the IVC could not be influenced by the cardiac events or the RA pressure. Second, reduction in right ventricular end-diastolic pressure during NP infusion indicated that contribution of the RA contraction to the right ventricle becomes less. Since the minimal flow velocity in the IVC usually occurs at the time of atrial contraction, and the minimal point is one of the determinants of the total amplitude of the velocity curve, the attenuation of the amplitude of the IVC flow velocity may result from the reduced RA contraction during NP. Third, in the present study, NP produced venous dilatation so that circulating volume might decrease during NP. Ishima et al. documented that acute hemorrhage caused a decrease in amplitude of the flow velocity curve of IVC in dogs, suggesting that reduction in the circulating volume may produce attenuation of the flow amplitude. These several factors could affect changes in the IVC flow velocity curve during NP.

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