PATHOPHYSIOLOGICAL CHARACTERISTICS OF LABILE HYPERTENSIVE PATIENTS DETERMINED BY THE COLD PRESSOR TEST*

EIKI MURAKAMI, KUNIO HIWADA, TATSUO KOKUBU

Hemodynamic changes during the cold pressor test were examined in Type I labile (juvenile labile) hypertensive patients, Type II labile (middle aged labile) hypertensive patients, established hypertensive patients and normal subjects. In normal, Type I labile hypertensive and established hypertensive subjects, the pressor response during the test was accounted for chiefly by a rise in peripheral resistance. In Type II labile hypertensive patients, an increase in blood pressure during cold stimuli was accompanied by an augmented cardiac output. Therefore, Type II labile hypertension is separated clearly from other types of hypertension with respect to hemodynamic changes during the test. In Type II labile hypertensive patients, however, diazepam reduced an increase in cardiac output during the test, resulting in hemodynamic changes similar to those of normal subjects. After atropinization, the hemodynamic pattern of Type I and established hypertensives changed similar to that of Type II labile patients during the cold pressor test.

It is concluded that an excessive cardiac output caused by the cold stimuli is a distinctive hemodynamic characteristics of Type II labile hypertensive patients, and this distinctive hemodynamic characteristics might be due to the decreased parasympathetic tone.

A simple and innocuous test to clarify the characteristics of hemodynamics in labile hypertensive patients is useful for the study of the pathophysiology of these patients. The cold pressor test has been available to examine sympathetic activity in hypertensive patients since its introduction by Hines and Brown!–2 Greene et al3 studied hemodynamic changes during the cold pressor test in patients with essential hypertension and stated that the cold pressor test was not reliable for separating hypertensive patients from normotensive subjects. Concerning the labile hypertension, Cuddy et al4 reported that hemodynamic patterns in labile hypertensive patients were variable than those in normal subjects during the test.

The purpose of this study is to characterize the hemodynamic differences during the cold pressor test among normotensive subjects, labile hypertensive patients and established hypertensive patients. In addition, we studied the effects of propranolol, diazepam and atropine on the hemodynamic changes of labile and established hypertensive patients during the test to see the role of autonomic nervous system in those patients.

SUBJECTS AND METHODS

(1) Subjects
(1) Normal controls: 16 male and a female

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Key Words:
- Cold pressor test
- Labile hypertension
- Cardiac output
- Total peripheral resistance
- Impedance cardiography

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TABLE I  HEMODYNAMIC CHANGES DURING THE COLD PRESSOR TEST

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>control values (at 0-time)</th>
<th>mean rise in the parameters during the cold pressor test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MBP (mmHg)</td>
<td>CO (L/min)</td>
</tr>
<tr>
<td>Normal</td>
<td>17</td>
<td>81.0 ± 2.0</td>
<td>5.93 ± 0.41</td>
</tr>
<tr>
<td>Type I labile hypertension</td>
<td>19</td>
<td>104.1 ± 2.2</td>
<td>5.07 ± 0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*(p &lt; 0.01)</td>
<td>*(p &lt; 0.001)</td>
</tr>
<tr>
<td>Type II labile hypertension</td>
<td>15</td>
<td>113.3 ± 3.2</td>
<td>5.04 ± 0.48</td>
</tr>
<tr>
<td>Established hypertension</td>
<td>25</td>
<td>122.7 ± 2.6</td>
<td>3.78 ± 0.25</td>
</tr>
<tr>
<td>All hypertensive patients</td>
<td>59</td>
<td>114.3 ± 1.8</td>
<td>4.51 ± 0.20</td>
</tr>
</tbody>
</table>

Values are the mean ± S.E.
Abbreviations: n = numbers of subjects, MBP = mean blood pressure, CO = cardiac output, TPR = total peripheral resistance
* Statistically significant compared with normal subjects

Subjects were volunteers (mean age, 35±3 years). They had no previous history of renal, cardiovascular or endocrine disease. All had casual blood pressure below 140/90 mmHg.

(2) Hypertensive patients: All hypertensive patients were in-patients in our hospital. Intravenous pyelography revealed no abnormality. The radioactive renogram was normal. Urinary catecholamines (noradrenaline and adrenaline) and vanillyl mandelic acid excretion rates were normal. We divided hypertensive patients into two groups, established essential hypertension and labile essential hypertension.

(a) Patients with established hypertension: 12 males and 13 females (mean age, 52 ± 2 years) in stage II according to WHO stage classification

(b) Patients with labile hypertension: labile hypertension in this study was defined as a blood pressure on admission was greater than 160/95 mmHg, and within the third hospital day, casual blood pressure reached in normal level without treatment. We further divided labile hypertensive patients into Type I and Type II labile hypertension.

Type I labile hypertensive patients (juvenile labile hypertensive patients): 16 males and 3 females (mean age, 29 ± 3 years) in stage I according to WHO stage classification.

Type II labile hypertensive patients (elderly patients who had some degree of vascular lesions): 5 males and 10 females (mean age, 49 ± 3 years) in stage II according to WHO stage classification.

Fig. 1. Changes of hemodynamic parameters during the cold pressor test.
A: normotensive controls
B: Type I labile hypertensive patients
C: Type II labile hypertensive patients
D: established hypertensive patients
Open circles or closed circles represent each mean value. Each bar represent ± S.E. In each group of the subjects, points are plotted at resting (at 0 time) and during cold immersion (at 60 sec).

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Fig. 2. Effects of propranolol and diazepam on hemodynamic changes during the cold pressor test.  
A: propranolol treatment  
B: diazepam treatment  
○-○ control study (without propranolol)  
●-● experimental study (with propranolol)  
△-△ control study (without diazepam)  
▲-▲ experimental study (with diazepam)  
Each bar represents ± SE. The statistical significances in ΔMBP, ΔCO and ΔTPR between the control and experimental studies are shown with asterisks: *, p < 0.02; **, p < 0.001.

(II) Test Procedures

All subjects were studied in the morning and had received no medication for a week before the test. The subjects were allowed to rest in a supine position in a quiet room at around 20°C for 30 min prior to the test. Then the hand was immersed to the wrist level in cold water (at 4°C) for 60 sec and the blood pressure was measured in the opposite arm. The blood pressure and cardiac output were recorded at rest just before the test (0 time) and at 60 sec after hand immersion in the cold water. Cardiac output was measured by impedance cardiography according to the method of Kubicek. There was a high correlation (r = 0.78, p < 0.001, n = 13) between the values for cardiac output measured by impedance cardiography and those measured by thermodilution method in our clinic. Mean blood pressure and total peripheral resistance were calculated from the following formulas:

Mean blood pressure (mmHg) = diastolic blood pressure + 1/3 pulse pressure

Total peripheral resistance (dyne·sec·cm⁻⁵) = mean blood pressure (mmHg)/cardiac output (ml/min) x 1322

Δ mean blood pressure, Δ cardiac output, and Δ total peripheral resistance (Δ = increase or decrease in values during the cold pressor test) were determined.
Propranolol and diazepam treatment

Effects of propranolol and diazepam on the hemodynamic changes in Type II labile hypertensive patients were studied. Paired studies (control and experimental) were performed in 6 patients. Control study (with no medication) was done as described above. Experimental study (with propranolol or diazepam) was done approximately one hour after the control study. Patients received 0.008 to 0.03 mg/min of propranolol by drip infusion. When 10% decrease in heart rate were recognized by cardiac monitor, the cold pressor test was performed in the manner described above. A few days later the same patients were given 10 mg of diazepam intravenously after the control study, and then the same test was done 5 min later.

Atropine treatment

Effect of atropine on the hemodynamic changes in hypertensive patients were studied. Five Type I labile, 6 Type II labile and 6 established hypertensive patients received 1.0 mg of atropine sulfate intravenously one hour after the control study. The test was again performed 5 min after atropinization.

Statistical evaluation

Student's t test or paired t test was used for statistical evaluation.

RESULTS

(1) Changes of mean blood pressure, cardiac output and total peripheral resistance during the cold pressor test

Table I and Fig. 1 show the results. In normal controls, Type I labile hypertensive patients and established hypertensive patients, there was little change in cardiac output during the test in spite of a rise in blood pressure. Pressor response produced only an increase in total peripheral resistance. However, in Type II labile hypertensive patients, an increase in cardiac output during the test was observed and the rise in blood pressure was caused mainly by an increase in cardiac output.

(II) Effects of propranolol and diazepam on hemodynamic changes during the cold pressor test in Type II labile hypertensive patients

Propranolol decreased the cardiac output of Type II labile hypertensive patients at rest, but did not decrease the cardiac output during the cold immersion. Diazepam showed the similar
effect on cardiac output at rest as propranolol. However, it markedly decreased the cardiac output during the test. Results are shown in Fig. 2. Type II labile hypertensive patients treated with diazepam showed the same hemodynamic changes as normal subjects and Type I labile and established hypertensive patients during the cold pressor test.

(III) Effect of atropine on hemodynamic changes during the cold pressor test in hypertensive patients

After treatment with atropine, the pressor response during the test was accompanied with a notable increase in cardiac output and little change of total peripheral resistance in hypertensive patients except for Type II labile hypertensive group. There was no difference in the hemodynamic response between Type I labile and established hypertensive patients. In Type II labile hypertensive patients, no remarkable change of hemodynamic pattern during the test was observed after atropinization (Fig. 3).

DISCUSSION

Our results demonstrated that the pressor response during the cold stimuli in normal subjects was associated with only an increase in peripheral resistance and cardiac output was almost unchanged. Our findings were essentially similar to those of Cuddy et al., but were contrary to those of Hejl et al. who showed that in normal subjects there was a rise in cardiac output and decrease in total peripheral resistance during the cold stimuli. On the other hand, in Type II labile hypertensive patients, there was an increase in cardiac output and no change in total peripheral resistance. Our observation that the response of blood pressure in Type II labile hypertensive patients was slightly higher than those in normal and Type I labile hypertensive subjects agreed with the findings by Voudoukins. The clinical features of Type II labile hypertensive patients were quite different from those of Type I labile hypertensive patients. Type II labile hypertensive patients showed a paroxysmally transient and severe elevation of blood pressure like patients with pheochromocytoma.

The cold pressor response is probably via a reflex of neurogenic arc involving the afferent spinthalamic tract and efferent sympathetic nervous system. Concerning the efferent sympathetic nervous system, it could be speculated that the pressor response in normal subjects and
essential hypertensive patients except Type II labile hypertensive patients might be due to α-adrenergic sympathetic stimuli. In contrast, in Type II labile hypertensive patients, β-adrenergic tone might be more predominant than α-adrenergic one. Results obtained, however, showed that propranolol did not decrease the response of cardiac output of Type II labile hypertensive patients.

The findings that there was no response in cardiac output during the cold pressor test in normal and hypertensive subjects except Type II labile hypertensives suggest a regulation via parasympathetic reflex. Atropinization caused the hemodynamic changes of those subjects similar to that of Type II labile hypertensive patients. A marked increase in cardiac output during the cold pressor test in Type II labile hypertensive patients is presumably due to weak parasympathetic tone.

We have experienced that a transient and severe hypertension in Type II labile essential hypertensive patients was well controlled by a minor tranquilizer. Although diazepam did not prevent the elevation of blood pressure in Type II labile essential hypertensive patients during the cold pressor test, it altered the cardiac responsiveness. Diazepam decreased the response of cardiac output and increased the total peripheral resistance during the test. The mechanism of diazepam that changes the hemodynamic pattern during the cold stimuli is unknown.

Our findings suggest that an excessive cardiac output caused by the cold pressor test and perhaps by emotional or other stresses is a distinctive hemodynamic characteristics of Type II labile essential hypertensive patients. This distinctive hemodynamic characteristics might be due to weak parasympathetic tone. The cold pressor test is a simple and good screening test for separating Type II labile hypertension from other types of essential hypertension.

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REFERENCE