Vasodepressor Effects of Prazosin during Insulin-Induced Hypoglycemia in Hypertensive Patients

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SUMMARY
As both hormonal and hemodynamic alterations similar to those occurring during exercise can also be produced in humans by hypoglycemia, the present study explored changes in hemodynamic parameters during hypoglycemia and the effects of the $\alpha$-adrenergic blocker, prazosin, on those responses in hypertensive patients. In the control group, which did not receive prazosin, plasma epinephrine, plasma norepinephrine and plasma renin activity (PRA) all increased along with a rise in blood pressure during hypoglycemia. On the other hand, the blood pressure decreased despite similar increases in plasma catecholamine levels and PRA in the prazosin treated group. The hemodynamic parameters, analyzed using M-mode echocardiography, changed in both the control and prazosin groups during hypoglycemia; stroke volume and cardiac output showed similar increases. However, while the total peripheral resistance did not change significantly in the control group, it decreased in the prazosin group during hypoglycemia. In accord with the changes in total peripheral resistance, the increment in mean-velocity of circumferential fiber shortening (m-Vcf) during hypoglycemia was greater in the prazosin group than in the control. These results suggest that: 1) hypoglycemia stimulates the sympatho-adrenal axis which then releases catecholamines leading to a rise in blood pressure and tachycardia; 2) In contrast, the blood pressure decreases during hypoglycemia in the prazosin group despite an increase in plasma catecholamines, because the $\alpha$-receptrons are blocked by prazosin and the unopposed $\beta$-adrenergic effects of the catecholamines are pronounced enough to reduce the total vascular resistance.

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HYPERTENSIVE hearts adapt to the abnormal, sustained hemodynamic burden that hypertension imposes by an increase in mass. This response maintains systemic perfusion despite the excessive load that, if it were applied acutely, might exceed the capacity of the normal heart. However, a hypertrophied heart is often unable to sustain this increased pressure overload for an indefinite period and heart failure may eventually supervene. In this respect, a reduction of the peripheral arterial resistance and the elimination of any additional hemodynamic burdens such as the vasoconstriction caused by sympathetic hyperactivity, is the ultimate aim of antihypertensive therapy to prevent heart failure.

The alpha-1 adrenergic blocker, prazosin, is now widely accepted as an antihypertensive drug; reflex tachycardia is not produced, which is in contrast to the effects of other vasodilators like hydralazine or phenoxybenzamine. One other characteristic effect of prazosin is that it may involve the blocking of the rise in blood pressure which accompanies exercise or mental stress. In this case prazosin antagonizes the effects of the catecholamines released from the sympathetic nerve terminals. However, this may lead to orthostatic hypotension, which can be an adverse effect of prazosin.

The present study was designed to investigate the effects of α-adrenergic blockade induced by prazosin on cardiovascular hemodynamics during exercise. However, although the hemodynamic changes during exercise include a rise in blood pressure and increased cardiac output, the actual recording of these parameters during exercise is sometimes difficult. Because the hemodynamics during exercise are possibly similar to those of the hypoglycemic state, as discussed later, we used this model, instead of exercise, to record hemodynamic alterations and to test the effects of prazosin on the responses of hypertensive patients.

MATERIALS AND METHODS

Two groups of non diabetic essential hypertensive patients (WHO stage I or II) were used; 7 untreated control patients (48±6 years old) and 8 prazosin treated patients (3 mg/day for more than 1 week, 52±4 years old). The humoral factors measured were blood sugar, plasma renin activity (PRA), plasma epinephrine (p-E) and plasma norepinephrine (p-NE). Blood pressure and heart rate were measured indirectly using an automatic sphygmo-
manometer (Nippon Korin Co Ltd, Tokyo). The hemodynamic parameters such as stroke volume, cardiac output and mean-Vcf were analyzed according to Gibson\(^{12}\) from an M-mode tracing from the left ventricular transection which was recorded by guidance using B-mode scanning (SSH-11A, Toshiba Electronics Co, Tokyo).

**Induction of hypoglycemia:** At 9:00 am the patients began bed rest. The blood pressure was measured from the right arm every 2 min. A drip infusion of physiological saline was started into the left antecubital vein. A three way valve through which venous blood was collected later, was attached between the needle and the connecting tube. At 9:30 am 15 ml of fasting blood were collected for determination of blood sugar, PRA, p-E and p-NE. This sample was taken via the three way valve so as not to cause stress to the patients. Right after the sampling, M-mode echocardiography was performed and the results recorded on the strip chart. Regular insulin (0.1 units/Kg, Shimizu Pharmaceutical Co Ltd, Shimizu, Japan) was then injected intravenously. The same procedures, as those initially done before insulin administration, were repeated 30 min after the administration of insulin. Later, 40 ml of 50% glucose solution were injected intravenously to restore euglycemia and the blood pressure was recorded until it had returned to baseline for more than 5 min.

Plasma concentrations of prazosin were measured before insulin administration using a sensitive, high-performance, liquid chromatography-fluorescence method.\(^{13}\)

Data expressed as an average ± SEM were compared using a paired or unpaired t-test and differences at a 5% level (p<0.05) were considered significant.

**Results**

Table I shows the control blood pressure, heart rate, blood sugar, PRA, p-E, p-NE, stroke volume, cardiac index, mean Vcf and total peripheral resistance in the 2 groups of hypertensive patients. None of these parameters was significantly different between the 2 groups.

Twenty min after insulin administration the patients began to complain of extreme hunger sensations. Approximately half of the patients then developed hyperhydrosis. Although most of the patients complained of palpitations during hypoglycemia, neither disturbance of consciousness nor arrhythmias developed.

The blood glucose level decreased from baseline by 62±3 mg/dl (the control group) and 58±4 mg/dl (the prazosin group) 30 min after insulin
Table I. Baseline Values in Control and Prazosin Treated Hypertensive Patients

<table>
<thead>
<tr>
<th>Variables measured*</th>
<th>Control</th>
<th>Prazosin</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 ± 6</td>
<td>59 ± 3</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>115 ± 7</td>
<td>102 ± 7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>61 ± 5</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>96 ± 7</td>
<td>100 ± 5</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>1.56 ± 0.51</td>
<td>2.01 ± 0.55</td>
</tr>
<tr>
<td>Plasma norepinephrine (ng/ml)</td>
<td>0.24 ± 0.03</td>
<td>0.26 ± 0.03</td>
</tr>
<tr>
<td>Plasma epinephrine (ng/ml)</td>
<td>0.05 ± 0.01</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>45.82 ± 5.82</td>
<td>45.90 ± 11.21</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>1.75 ± 0.30</td>
<td>1.67 ± 0.42</td>
</tr>
<tr>
<td>Mean-Vcf (circ/sec)</td>
<td>0.90 ± 0.10</td>
<td>0.95 ± 0.08</td>
</tr>
<tr>
<td>Total peripheral resistance (dyn·sec/cm²)</td>
<td>2620 ± 431</td>
<td>2922 ± 393</td>
</tr>
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</table>

* None of the variables measured were significantly different between the control and prazosin groups.

Fig. 1. Blood pressure responses to hypoglycemia in the control and prazosin-treated hypertensive patients. Abbreviations: C=control; P=prazosin; 0=before the injection of insulin; 30'=30 min following the insulin injection; POST=following intravenous injections of glucose, 20 g. *Significant by unpaired t-test (control vs prazosin).

administration as shown in Table I. The difference between the groups was not significant. Fig. 1 shows the changes in blood pressure during the study; in the control group, the blood pressure level during hypoglycemia was significantly higher than either the baseline in the pre-insulin period (p<0.01, paired t-test) or the post-glucose supplement period (p<0.01); by contrast, in the prazosin-treated group, the blood pressure decreased significantly (p<0.01) during hypoglycemia. The heart rate then increased slightly (+9.6±1.8 beats/min in the control and +7.7±3.2 beats/min in the prazosin
Fig. 2. Responses of plasma renin activity (PRA), norepinephrine (NE) and epinephrine (E) on hypoglycemia in the control (C) and prazosin-treated (P) groups. No significant differences were found between the 2 groups in all variables.

Fig. 3. Increments of stroke volume (SV), cardiac index (CI) and mean-velocity of circumferential fiber shortening (m-Vcf) in the control (C) and prazosin (P) groups (*p<0.05 with unpaired t-test).

group), though the difference was not significant. The increment in PRA was almost the same in both the control and the prazosin groups (Fig. 2). Nor were the differences between the control group and the prazosin group in the increase in levels of both p-E and p-NE during hypoglycemia significant (Fig. 2). Fig. 3 shows the increments of stroke volume, cardiac index and m-Vcf. Both stroke volume and cardiac index increased under hypoglycemic stress. Of the changes, only the increase in m-Vcf was significantly (p<0.05) greater in the prazosin group than in the control. Total peripheral resistance
was calculated from the blood pressure and cardiac output in each of the patients. Although the total peripheral resistance did not change significantly under hypoglycemic stress in the control group (from 2710±472 to 2546±498 dyn·sec/cm⁵), it did decrease significantly in the prazosin group (from 2912±406 to 2118±384 dyn·sec/cm⁵, p<0.05).

To confirm the administration of prazosin, the plasma levels of prazosin were measured in 4 control and 5 prazosin-treated patients. While the level was under the maximal sensitivity of the assay system (less than 0.3 ng/ml) in the control group, it was significantly higher in the prazosin group (33±2 ng/ml).

**DISCUSSION**

The present study revealed that hypoglycemia elevates blood pressure by increasing cardiac output. The rise in blood pressure, the accompanying tachycardia, and the increase of stroke volume and cardiac output resemble the hemodynamic alterations which occur during exercise. Because these alterations are accompanied by increases in plasma catecholamine levels, the hemodynamic changes recorded could be attributed to stimulation of the adrenergic receptors. It is suggested that hypoglycemia activates the hypothalamic sympathetic vasomotor center to increase peripheral sympathetic outflow. The rise in norepinephrine, dopamine beta-hydroxylase and plasma renin activity indicates increased peripheral sympathetic outflow during hypoglycemia.

Plasma concentrations of both norepinephrine and epinephrine also increase along with an increase in the intensity and duration of dynamic exercise. During maximal dynamic exercise in normal young subjects, plasma norepinephrine may increase from 1.40 to 20 nmol/l while epinephrine increases from 0.25 to 2 nmol/l. These increments are believed to be due almost entirely to increased release of catecholamines, rather than to a reduced rate of tissue uptake. On the other hand, during less severe exercise, such as isometric exercise, only small increments in plasma norepinephrine are found. Nevertheless, the arterial blood pressure rises considerably, owing to the rise in cardiac output. Interestingly, the rise in plasma epinephrine, relative to that of norepinephrine, is larger during isometric exercise than during dynamic exercise. These observations during isometric exercise resemble the finding that hypoglycemia increased the catecholamine levels in the present study. Several lines of evidence suggest that sympathoadrenal activity plays a major role in the mobilization of metabolic substrate during exercise; in humans, mobilization of fuel depots is probably caused by the
direct effects of increased sympathetic nervous system activity and its inhibitory influence on insulin release.\textsuperscript{21}-\textsuperscript{28}) Thus, exercise influences glucose metabolism via hormone release; i.e., exercise activates the sympathoadrenal system to increase the plasma glucose level in order to maintain the energy source. On the other hand, during insulin-induced hypoglycemia, the sympathoadrenal system is supposed to be stimulated, as during exercise, to increase the plasma glucose level. The common phenomenon of an elevated sympathoadrenal system activity seems to result in similar changes in the hemodynamic parameters during both exercise and hypoglycemia.

Pretreatment with prazosin abolished the pressor responses and, on the contrary, produced depressor responses when hypoglycemia was achieved; blood pressure fell due to a reduction in total peripheral resistance, despite increments in stroke volume, heart rate and cardiac output similar to that observed in those patients not receiving prazosin. Similarly, hypotension during exercise has been reported in hypertensive patients treated with prazosin.\textsuperscript{29}) These results indicate that both decreased peripheral resistance and increased m-Vcf, an index of cardiac contractility, can be attributed to an augmented \( \beta \)-adrenergic mechanism induced by prazosin, because prazosin blocks only the postsynaptic \( \alpha \)-adrenergic receptors.\textsuperscript{10,30}) Factors which influence the m-Vcf include a decrease in the afterload of the heart and a \( \beta \)-adrenergic agonistic action of the catecholamines. The greater increase in m-Vcf in the prazosin group than in the control group was due mainly to the decrease in peripheral resistance (afterload) in the prazosin group. However, the inotropic actions of catecholamines due to the increased catecholamine levels would also be greater in the prazosin group than in the control group because the \( \beta \)-receptors would have been stimulated relatively more in the prazosin group due to \( \alpha \)-adrenergic blockade. This may also lead to an increased m-Vcf. These findings support the concept that prazosin is effective in the treatment of heart failure.\textsuperscript{31}-\textsuperscript{34})

Because prazosin administration decreased peripheral vascular resistance during hypoglycemia without decreasing cardiac output, the tissue perfusion rate is maintained even when the blood pressure is decreased during hypoglycemia. Thus, we conclude that prazosin has beneficial effects on the hemodynamic alterations during hypoglycemia and possibly during exercise.

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