Increased Plasma Norepinephrine Accompanies Persistent Tachycardia After Hydralazine

MIN-SHUNG LIN, M.D., JOHN L. MCNAY, M.D., ALEXANDER M. M. SHEPHERD, M.D., PH.D., GARY E. MUSGRAVE, PH.D., AND T. KENT KEETON, PH.D.

SUMMARY To determine the role of the peripheral sympathetic nervous system in the persistent tachycardia caused by the antihypertensive drug hydralazine, we examined the temporal relationships between the changes in heart rate and plasma norepinephrine concentration and the reduction in blood pressure produced by a range of doses of hydralazine administered intravenously to five hypertensive patients. Significant linear correlations were found between the increases in heart rate and plasma norepinephrine concentration and the reduction in blood pressure at 15 and 30 minutes after injection. However, at 240 minutes after injection, changes in heart rate and plasma norepinephrine were not correlated with changes in blood pressure and were disproportionately elevated relative to the reduction in blood pressure. A significant linear correlation between changes in heart rate and plasma norepinephrine concentration was noted at 15, 30, and 240 minutes after injection. The temporal discordance of the changes of both heart rate and plasma norepinephrine relative to the reduction in blood pressure and the significant linear correlation between the increases in heart rate and plasma norepinephrine concentration suggest that continued activation of the peripheral sympathetic nervous system contributes to the persistent tachycardia seen after the administration of hydralazine. (Hypertension 5: 257-263, 1983)

KEY WORDS • sympathetic nervous system • heart rate • vasodilation

THE decrease in blood pressure (BP) caused by the peripheral vasodilator hydralazine is associated with an increase in heart rate (HR)1,2. The tachycardia is of clinical importance since it favors an increase in cardiac output, which would tend to offset the antihypertensive effect of hydralazine. Accordingly, suppression of hydralazine-induced tachycardia by the coadministration of beta-adrenoceptor antagonists is believed to contribute to the increased efficacy of this combined drug therapy in the treatment of hypertension.3,4 In addition, the increase in myocardial oxygen consumption associated with the tachycardia may precipitate myocardial ischemia in the presence of atherosclerotic heart disease.5

Although the increase in HR caused by hydralazine can be attributed in part to activation of the arterial baroreflexes in response to a reduction in BP, researchers have recognized that the increase in HR persists disproportionately longer than the vasodepressor effect.6 In addition, several investigators7-8 have demonstrated that restoration of the systemic BP to normal by the infusion of vasodepressor agents does not completely reverse the tachycardia seen after administration of hydralazine to animals. Thus, arterial baroreflex activation of the peripheral sympathetic nervous system cannot completely account for the persistent tachycardia caused by hydralazine.

Although plasma norepinephrine (NE) concentration is known to be increased following administration of hydralazine to animals,9 the quantitative relationship between the increase in plasma catecholamine levels and the reduction in BP has not been defined in humans. In particular, the time course of the elevation of plasma NE concentration relative to hydralazine-induced vasodepression has not been evaluated. In addition, the relationship between the increase in HR and the increase in plasma catecholamine levels has not been determined. The latter relationship is of particular interest since the increase in HR that occurs during a reduction in arterial pressure with diazoxide appears to result from both increased sympathetic neuronal activity and decreased vagal activity.10

To study the role of the peripheral sympathetic nervous system in the persistent tachycardia caused by hy-
intravenous catheter was inserted in the right forearm vein for blood sampling. Blood pressure was measured from the right arm using an Arteriosonde recorder (Hoffman-La Roche, Cranbury, New Jersey). The electrocardiogram was displayed continuously on an oscillograph, and HR was counted from a 1-minute strip recording. From 0730, BP and HR were measured at 10-minute intervals. At 0930, hydralazine was infused intravenously as a square-wave injection over a period of 100 seconds, after which BP and HR were measured every 5 minutes for 1 hour and then every 10 minutes for an additional 3 hours.

**Methods**

**Subjects**

Our subjects were five men (one black, four white) aged 40–50 years, with essential hypertension of 5 to 10 years’ duration. Each patient was followed regularly in the hypertension clinic at the Audie Murphy Veterans Administration Hospital in San Antonio. Each patient had been receiving hydralazine, propranolol, and hydrochlorothiazide to control their hypertension for greater than 6 months. None of the patients exhibited any clinical evidence of angina pectoris, myocardial infarction, diabetes mellitus, congestive heart failure, renal disease, or peripheral neuropathy. Except for Keith-Wagner grade I–II retinopathy, no physical abnormalities were detected. Routine biochemical, hematologic, radiologic, and electrocardiographic measurements were within normal limits. Each subject provided informed consent on forms approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

**Protocol**

All antihypertensive medications except hydrochlorothiazide were discontinued 1 week before admission. Patients were then admitted to the Special Diagnostics and Treatment Unit at the Audie Murphy Veterans Administration Hospital. After admission, 3 to 4 days were allowed for acclimatization to the hospital environment. Salt intake was fixed at 137 mEq per day, and coffee and tea were not allowed. A 50 mg dose of hydrochlorothiazide was administered at 7:00 a.m. each hospital day except on study days (see below) when it was administered at 1:00 p.m. Although sodium balance was not monitored, no significant change in body weight was detected during the period of hospitalization.

During the hospitalization, each patient was given intravenous injection of four different doses of hydralazine, ranging from 0.05 to 0.6 mg/kg. The order of administration of the different doses was varied among patients. The different doses of hydralazine were administered at least 3 days apart to allow the effects of the previous dose to subside. The 0.2 and 0.3 mg/kg doses of hydralazine were administered to each patient, and the size of the remaining doses were predetermined on the response of each patient to these two standard doses.

On study days starting at the previous midnight, the patient had nothing by mouth except water. The patients remained recumbent throughout the study. At 0700, a pediatric scalp vein needle with a heparin lock was placed in the left forearm vein for the administration of 5% glucose in water and hydralazine. A second ivavenous injection of four different doses of hydralazine, ranging from 0.05 to 0.6 mg/kg. The order of administration of the different doses was varied among patients. The different doses of hydralazine were administered at least 3 days apart to allow the effects of the previous dose to subside. The 0.2 and 0.3 mg/kg doses of hydralazine were administered to each patient, and the size of the remaining doses were predetermined on the response of each patient to these two standard doses.

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TABLE 1. Chronology of the Changes in Mean Arterial Pressure (MAP), Heart Rate (HR), Plasma Norepinephrine (NE) Concentration, and Epinephrine (E) Concentration Seen after the Intravenous Injection of 0.2 mg/kg of Hydralazine into Five Recumbent Hypertensive Patients

<table>
<thead>
<tr>
<th>Minutes after injection</th>
<th>0 (Baseline)</th>
<th>15</th>
<th>30</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>102 ± 5</td>
<td>95 ± 4*</td>
<td>94 ± 4*</td>
<td>100 ± 6</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>69 ± 4</td>
<td>80 ± 4*</td>
<td>82 ± 3*</td>
<td>81 ± 6*</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>196 ± 17</td>
<td>265 ± 12†</td>
<td>299 ± 11*</td>
<td>300 ± 29*</td>
</tr>
<tr>
<td>EP (pg/ml)</td>
<td>28 ± 4</td>
<td>59 ± 32</td>
<td>49 ± 13</td>
<td>100 ± 36*</td>
</tr>
</tbody>
</table>

*p < 0.01.
†p < 0.05.
All values are the means ± SEM.

TABLE 2. Chronology of the Changes in Mean Arterial Pressure (MAP), Heart Rate (HR) and Plasma Norepinephrine (NE) Concentration, and Epinephrine (EP) Concentration Seen after the Intravenous Injection of 0.3 mg/kg of Hydralazine into Five Recumbent Hypertensive Patients

<table>
<thead>
<tr>
<th>Minutes after injection</th>
<th>0 (Baseline)</th>
<th>15</th>
<th>30</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>108 ± 4</td>
<td>99 ± 3*</td>
<td>98 ± 3*</td>
<td>103 ± 2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67 ± 4</td>
<td>86 ± 2†</td>
<td>88 ± 3†</td>
<td>88 ± 5†</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>291 ± 50</td>
<td>404 ± 79</td>
<td>435 ± 63</td>
<td>545 ± 110*</td>
</tr>
<tr>
<td>EP (pg/ml)</td>
<td>44 ± 15</td>
<td>53 ± 10</td>
<td>53 ± 10</td>
<td>133 ± 47*</td>
</tr>
</tbody>
</table>

*p < 0.05.
†p < 0.01.
All values are the means ± SEM.

Large as those observed at 15 and 30 minutes after injection. Thus, both HR and plasma NE concentration remained elevated at a time when MAP was not decreased significantly relative to the baseline value. Although no significant rise in plasma E concentration was seen at 15 and 30 minutes after injection, a 2.6-fold increase (p < 0.01) was observed at 240 minutes after injection.

Similar results were obtained with the 0.3 mg/kg dose of hydralazine (table 2). This dose of hydralazine caused a significant decrease in MAP at 15 and 30, but not at 240, minutes after injection. The HR was elevated to the same extent at all times. Plasma NE concentration increased progressively over the 240 minutes after hydralazine injection. In fact, the increase in plasma NE concentration at 240 minutes (+87%) was larger than the increase seen at 30 minutes (+49%) despite the fact that the MAP was not decreased significantly from the baseline values at 240 minutes after injection. As before, plasma E concentration was increased significantly at 240 minutes, but not at 15 or 30, minutes after injection.

Highly significant linear relationships were seen between ΔHR and ΔMAP at 15 and 30 minutes, but not at 240 minutes, after injection (fig. 1). The slopes of the regression lines relating ΔHR to ΔMAP at 15 and 30 minutes after injection were not significantly different. The increases in HR at 240 minutes were large relative to the decreases in MAP, particularly in the lower range of ΔMAP. Thus, the increase in HR caused by hydralazine tended to persist even though the MAP had returned toward the baseline values.

At 15 and 30 minutes after injection, a significant linear correlation was noted between ΔNE and ΔMAP, but no significant correlation was seen at 240 minutes (fig. 2). The slopes of the regression lines relating ΔNE to ΔMAP at 15 and 30 minutes after injection were not significantly different. As with the changes in

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** FIGURE 1.** Relationships between changes in heart rate (ΔHR) and mean arterial pressure (ΔMAP) at 15, 30, and 240 minutes after intravenous administration of four doses of hydralazine to five hypertensive patients. The data from individual patients are identified by the symbols: C (●), M (▲), B (○), P (Δ), S (■).
HR, the increases in plasma NE concentration at 240 minutes were large relative to the decreases in MAP, particularly in the lower range of ΔMAP.

As shown in figure 3, a highly significant linear correlation existed between ΔHR and ΔNE at 15, 30, and 240 minutes after giving hydralazine. However, the slope of the regression line at 240 minutes was significantly less than that calculated at 15 and 30 minutes after injection. At 15 and 30 minutes after injection, the slopes of the regression lines relating ΔHR to ΔNE were not significantly different.

At no time after injection was ΔEP correlated with ΔMAP or ΔHR.

Discussion

We found that the activity of the peripheral sympathetic nervous system, as quantified by plasma NE concentration, increased progressively over the 240 minutes after the administration of hydralazine despite a significant recovery of BP toward the control value during this time. Accordingly, the relationship of ΔNE to ΔMAP increased markedly with time. Although a significant correlation was noted between ΔNE and ΔMAP at 15 and 30 minutes after hydralazine injection, this correlation was lost at 240 minutes. The latter observation suggests that, under the conditions of this study, some factor(s) other than the magnitude of the
pressure stimulus to the high-pressure baroreceptors is responsible for the persistent elevation of plasma NE caused by hydralazine. It should be pointed out that the progressive increase in plasma NE concentration relative to the vasodepressor response was not dependent on the dose of hydralazine or the magnitude of the maximal fall in BP since this phenomenon was observed over a range of doses and vasodepressor responses within the same group of patients.

The persistent elevation of plasma NE concentration seen after the administration of hydralazine could result from: 1) a diurnal variation in baroreflex sensitivity; 2) a change in the clearance of NE from the plasma; 3) an alteration by hydralazine of the afferent signals from the high-pressure baroreceptors; or 4) a direct effect of hydralazine on the neuronal release of NE.

Primary consideration must be given to the possibility that the change in the relationship of ΔNE to ΔMAP was due to the passage of time per se. In an independent study of the effects of sodium nitroprusside-induced vasodepression on plasma NE concentration in hypertensive patients, no differences in BP, HR, or plasma NE concentration were noted between 0930 and 1330 even though in the intervening period BP had been decreased for 90 minutes with sodium nitroprusside (0930 to 1100) (Lin M-S, unpublished observations). These data confirm a previous report in which patients also receiving hydrochlorothiazide showed a recumbent BP and plasma NE concentration that was approximately equal at 0900 and 1300. However, despite similar values for unstressed blood and plasma NE concentration at 0930 and 1330, the response of BP and plasma NE concentration to peripheral vasodilators may be affected by the time of day. Hossman et al. have shown that baroreflex sensitivity in normotensive humans is increased at 1200 relative to 0900. In addition, the slope of the dose-response curve for the pressor effects of infused NE was reduced at 1200 relative to 0900. We have shown that when individual hypertensive patients are compared, an increase in baroreflex sensitivity is associated with a greater rise in plasma NE concentration for any given reduction in BP. If this same relationship holds true within individual patients at different times of the day, and if the prolonged vasodepression caused by hydralazine did not alter the diurnal variation in baroreflex sensitivity, then the increased baroreflex sensitivity at 1200 relative to 0900 may be responsible in part for the continued increase in plasma NE concentration seen at 4 hours after injection (1330) relative to 15 minutes after injection (0945). It should be pointed out that the studies of Hossman et al. were conducted with normotensive humans, and equivalent temporal changes in baroreflex sensitivity may not occur in hypertensive patients.

The concentration of NE in the plasma depends on both its rate of secretion into the plasma and its clearance from the plasma. It is possible that the relative magnitude of the rates of secretion and clearance of plasma NE may have changed during the 4 hours after the injection of hydralazine. Because the liver has been shown to extract NE from the plasma, a rapid recovery of the hepatoportal circulation from the vasodilatory effects of hydralazine would lead to a decrease in hepatic blood flow and thus a decrease in the hepatic clearance of plasma NE. That is, if hepatoportal vascular resistance recovered more rapidly from the vasodilatory effects of hydralazine than did total peripheral resistance, the hepatic clearance of plasma NE would decrease at the same time that continued reflex activation of the sympathetic nervous system was maintaining the secretion of NE at a level higher than normal. This hypothesis is consistent with the observed decrease with time in the slope of the ΔHR/ΔNE relationship since the concentration of NE at the cardiac neuroeffector junction would remain unaffected even though the plasma NE concentration would increase, i.e., plasma NE concentration relative to its rate of release would increase. Although the time course of the changes in regional blood flow relative to the reduction in BP after hydralazine has not been studied in humans, studies conducted with dogs indicate that mesenteric vasodilation may be shorter in duration than is renal vasodilation.

Hydralazine may alter afferent discharge from the high-pressure baroreceptor so as to increase sympathetic neuronal function relative to any given level of BP. Safir et al. have shown that the decrease in BP in hypertensive patients treated with hydralazine is associated with a decrease in the diameter of the brachial artery. The rate of discharge of afferent fibers originating in the high-pressure baroreceptors is proportional to tangential (circumferential) wall stress, which is itself proportional to the product of arterial pressure and the internal radius of the vessel. If hydralazine also decreased the diameter of the carotid artery, a decrease in the rate of firing of the afferent fibers and thus an increase in peripheral sympathetic nerve activity disproportionate to the level of BP would occur. Finally, we must consider the possibility that hydralazine has a direct effect on the release of NE from the sympathetic neuron. The treatment of rats with hydralazine was found to result in the depletion of NE in the heart and but had no effect on catecholamine stores in the mesenteric artery or vein. Ganglionic blockade blunted, but did not abolish, the ability of hydralazine to lower cardiac NE levels. Khatri et al. reported that the direct injection of hydralazine into a coronary artery of anesthetized dogs caused a localized increase in myocardial contractility which was blocked by the intravenous administration of propranolol. Spokas and Wang found no localized change in myocardial contractility when equivalent doses of hydralazine were injected into a coronary artery of anesthetized dogs. In conclusion, hydralazine appears to possess only weak tyramine-like properties.
10 Hz. Even if hydralazine did suppress the release of NE by a direct action on the sympathetic neuron, this effect cannot serve to explain the persistent increase in plasma NE concentration seen after the administration of hydralazine.

Although a decrease in the hepatic clearance of plasma NE might account for the persistent increase in plasma NE concentration relative to the vasodepressor effect of hydralazine, such a mechanism would not account for either the observed loss of the correlation between ΔHR and ΔBP or the persistent elevation of HR relative to the vasodepressor effect at 240 minutes after injection. Diurnal variation in baroreflex sensitivity might partially account for the persistent tachycardia, but some factor(s) other than the level of BP at the high-pressure baroreceptors must account for the persistent increase in HR seen as BP returns toward the baseline value.

This conclusion is consistent with the observation that the restoration of BP to prehydralazine values by the infusion of vasodepressor agents did not completely reverse the tachycardia seen after the administration of hydralazine to animals. The known effect of hydralazine to increase venous return would serve to increase HR by activation of atrial stretch receptors, i.e., activation of the Bainbridge reflex (see ref. 7 for a discussion). In fact, it is generally recognized that vasodilator drugs which cause arteriolar dilation without affecting venous tone cause a greater increase in HR than do drugs which dilate both resistance and capacitance vessels. If the increase in venous return caused by hydralazine persisted longer than the arteriolar dilation, then a portion of the persistent tachycardia could be due to activation of the Bainbridge reflex.

The disproportionate increase in HR at 240 minutes after hydralazine clearly is associated with an increase in plasma NE concentration since a significant correlation exists between ΔHR and ΔNE. These results are consistent with the correlation between the concentration of NE in plasma obtained from the coronary sinus and the increase in HR caused by stimulation of the stellate ganglia in anesthetized dogs. In addition, Graham et al. found a similar relationship between ΔHR and ΔNE after the intravenous administration of hydralazine to conscious rats. Unfortunately, the contribution of withdrawal of vagal tone to the increase in HR cannot be estimated in our studies. The importance of the withdrawal of vagal tone in the reflexly-induced tachycardia caused by vasodilator drugs has been demonstrated in humans and animals. Although our observations of a consistent correlation between ΔHR and ΔNE provides evidence for a role of the sympathetic nervous system in the persistent tachycardia seen after hydralazine, a decrease in cardiac parasympathetic nerve activity also probably occurs.

The progressive decrease with time in the slope of the relationship of ΔHR to ΔNE is of interest. This progressive decrease may be due to: 1) the postulated decrease in the hepatic clearance of plasma NE; 2) rapid desensitization of cardiac receptors to the chronotropic effect of NE, or 3) a direct chronotropic effect of hydralazine on the heart. If the latter effect occurs at plasma concentrations produced in humans, the concentration of hydralazine at 15 and 30 minutes relative to that at 240 minutes might contribute to the greater ΔHR/ΔNE at the earlier times.

Even though E is a more potent agonist at beta-adrenergic receptors than NE, no correlation was found between the changes in HR and the changes in plasma E concentration after BP was lowered with hydralazine. In addition, if ΔE had been contributing to the increase in HR at 240 minutes, a steeper ΔHR/ΔNE slope would have been expected rather than the flatter slope observed. The threshold of plasma E necessary to increase HR has been estimated to be 50 to 100 pg/ml. Thus, the rise in the plasma concentration of E seen in this study may not have been of sufficient magnitude to increase HR. The mechanism of the late increase in plasma E concentration after hydralazine is unknown, but this increase may be related to a decrease in the systemic clearance of plasma E.

It should be noted that the patients in the present study were receiving a thiazide diuretic, and the administration of thiazide diuretics has been reported to elevate the plasma concentration of NE. The elevation of the basal levels of plasma NE may possibly affect the increase in plasma catecholamine content caused by hydralazine, but this possibility does not detract from the present observations since, from a practical viewpoint, nearly all patients who receive hydralazine also will be receiving a diuretic.

In summary, even though these studies were performed in a small number of patients, they indicate that a quantitative relationship exists between the vasodepressor effect of hydralazine, the augmentation of plasma NE concentration and the increase in HR during the first half hour after the intravenous administration of hydralazine. Over the subsequent 210 minutes, however, a progressive increase in the plasma concentration of NE occurs relative to the vasodepressor effect, and the linear relationship of ΔNE to ΔMAP is lost. We suggest that the increase in the relationship of ΔNE to ΔMAP may reflect a time-dependent decrease in the rate of clearance of NE from the plasma, but such a mechanism cannot account for the persistent tachycardia caused by hydralazine. Since a close relationship is observed between ΔHR and ΔNE at all time periods, it is possible that baroreflex function has been potentiated.

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