Cardiovascular Responses to Isometric Exercise and Standing in Normotensive Subjects During Converting Enzyme Inhibition with Teprotide

ANDREAS P. NIARCHOS, M.D., THOMAS G. PICKERING, M.D., AND JOHN H. LARAGH, M.D.

SUMMARY The hemodynamic responses to isometric exercise (hand grip) were investigated in normotensive subjects during a 150 mEq (n = 8) sodium diet and a 10 mEq (n = 6) sodium diet both before and after the administration of the converting enzyme inhibitor teprotide. Although teprotide significantly decreased the mean arterial pressure during both sodium intakes, the normal pattern of hemodynamic response to hand grip was preserved, that is mean arterial pressure was increased by hand grip mainly because of an increase in cardiac output. Changes of plasma catecholamines during hand grip were not affected by teprotide. In addition, the hemodynamic responses to standing were not substantially altered by teprotide. When fainting occurred (in the seated position) following the administration of teprotide, it was associated not only with a decrease in arterial pressure but also with a concurrent reduction in cardiac output. We conclude that angiotensin inhibition by teprotide does not significantly impair sympathetically mediated cardiovascular responses.

KEY WORDS • renin-angiotensin II system • normal blood pressure • catecholamines • normal or low sodium intake • converting enzyme inhibition • cardiovascular reflexes

SEVERAL recent studies have provided evidence that the renin-angiotensin-aldosterone system participates in the pathogenesis of elevated arterial pressure in renovascular and essential hypertension in humans and in some experimental forms of hypertension in animals. This pathogenetic role of the renin-angiotensin system has now been investigated more precisely as a result of the availability of pharmacological tools that block the renin-angiotensin system in several sites. These agents include the angiotensin II competitive antagonist, saralasin, the converting enzyme inhibitors, teprotide and captopril, which block the conversion of angiotensin I to angiotensin II, and more recently the antirenin antibodies and the renin-inhibiting peptides, which antagonize renin per se. Although these antagonists have additional pharmacological effects, it is generally agreed that the cardiovascular effects of saralasin and of the converting enzyme inhibitors and those of the antirenin agents are mainly due to their ability to interrupt the renin-angiotensin system.

On the other hand, the role of the renin-angiotensin system in regulating normal arterial pressure in normotensive subjects has been little investigated. Sancho and associates administered the converting enzyme inhibitor teprotide to normotensive subjects and concluded that the renin-angiotensin system is essential for the maintenance of normal blood pressure only during sodium depletion. However, other more recent studies have demonstrated that, even during normal sodium intake, converting enzyme inhibition with teprotide or captopril results in a decrease in arterial pressure in normotensive subjects.

The purpose of our present study was to elucidate further the possible role of the renin-angiotensin system in normal blood pressure regulation. We investigated mainly the possible interaction of the renin-angiotensin system with the sympathetic nervous system...
and sodium and volume factors, and the possibility that blockade of the renin-angiotensin system affects the cardiovascular response to stimuli such as isometric exercise or assuming the upright posture, which activate the sympathetic nervous system. Further, we also investigated the hemodynamic mechanism of fainting during converting enzyme inhibition.

Methods

Eight normotensive subjects whose ages ranged from 26 to 53 years were admitted to the Clinical Research Center after giving their informed consent to the study. They were placed on a 150 mEq sodium diet and 60 mEq potassium diet, and after 5 to 6 days when metabolic balance had been achieved, they underwent the following investigations.

The subject remained in the seated position for at least 1 hour after the insertion of arterial and venous lines, to allow for stabilization of arterial pressure and heart rate. Cardiac output was measured by dye dilution, arterial pressure by an intraarterial catheter, and blood was drawn for the measurement of plasma renin activity by radioimmunoassay and plasma catecholamines by the radioenzymatic method. (With the radioenzymatic method, plasma catecholamine levels as low as 5 pg/ml may be detected.) Then teprotide (SQ 20,881) was given intravenously as a bolus in its usual antihypertensive dose of 1 mg/kg body weight, and all investigations were repeated 30 minutes later. Then an isometric hand-grip test was performed for 3 minutes at 30% of maximum voluntary contraction, and all measurements were repeated during the third minute of the hand-grip test. Next was a control period to allow the heart rate and blood pressure to return to the basal levels. After this period, which was usually 10 to 15 minutes, the subjects were asked to assume the upright posture and stand quietly for 5 minutes, and the blood pressure transducers were readjusted to the new position. Cardiac output, arterial pressure, and heart rate were recorded, and blood was taken again for the renin and catecholamine measurements. Then the study was terminated. After this first study, six subjects were placed on a 10 mEq sodium diet, and all investigations were repeated 5 to 6 days later, under the same conditions and in the same order, namely, control measurements in the seated position, followed by measurements after the administration of teprotide, hand grip for 3 minutes, control period, and then standing for 5 minutes.

The paired and unpaired t test, as appropriate, was used in the statistical analysis of the results (given as means ± SEM). A p value of less than 0.05 was accepted as significant, but for the changes in catecholamines, a two-tailed (2 t) p value of less than 0.05 was accepted as significant. Correlation coefficient values were calculated by the method of Spearman. Derived parameters (stroke volume and total peripheral resistance) were calculated from standard equations.

Results

Hemodynamic and Humoral Effects of Teprotide During Sodium Intake of 150 and 10 mEq

The hemodynamic and humoral effects of teprotide 30 minutes after its administration during the 150 mEq (n = 8) and 10 mEq (n = 6) sodium intake are summarized in table 1. The decrease in mean arterial pressure by teprotide was caused by the decrease in peripheral resistance (table 1), and this effect was more

| Table 1. Hemodynamic and Humoral Effects of Sodium Depletion and Teprotide in Normotensive Subjects |
|---------------------------------|----------------|----------------|----------------|
|                                | 150 mEq (n = 8) | 10 mEq (n = 6) |
|                                | Control         | 30 min after teprotide | Control         | 30 min after teprotide |
|                                | HR (mm Hg)      | 65 ± 3          | 67 ± 3          | 69 ± 5          | 72 ± 6          | NS |
|                                | MAP (mm Hg)     | 75 ± 3          | 65 ± 3(5)       | < 0.01          | 69 ± 2          | 56 ± 3          | < 0.005        |
|                                | SV (ml/beat)    | 73 ± 7          | 72 ± 8          | NS              | 55 ± 5*         | 62 ± 4          | < 0.05         |
|                                | CO (liter/min)  | 4.72 ± 0.36     | 4.82 ± 0.42     | NS              | 3.91 ± 0  33*   | 4.40 ± 0.3      | < 0.005        |
|                                | TPR (units)     | 17 ± 1          | 14 ± 1          | < 0.05          | 18 ± 1*         | 12 ± 1          | < 0.005        |
|                                | PRA (ng/ml/hr)  | 2.0 ± 0.4       | 5.2 ± 1 27      | < 0.01          | 7.36 ± 1.3*     | 31 ± 4          | < 0.025        |
|                                | EPI (pg/ml)     | 74 ± 15         | 90 ± 24         | NS              | 64 ± 10         | 91 ± 14         | NS |
|                                | NEPI (pg/ml)    | 301 ± 35        | 332 ± 58        | NS              | 367 ± 109       | 358 ± 83        | NS |
|                                | UNaV (mEq/24 hr)| 136 ± 6         | —               | 13 ± 4*         | —               | —               | — |
|                                | UA (µg/24 hr)   | 10 ± 2          | —               | 36 ± 7*         | —               | —               | — |
|                                | UKV (mEq/24 hr) | 66 ± 6          | —               | 67 ± 8          | —               | —               | — |
|                                | Wt (kg)         | 74.15 ± 3.44    | 72.87 ± 3.51*   | —               | —               | —               | — |

HR = heart rate, MAP = mean arterial pressure; SV = stroke volume; CO = cardiac output; TPR = total peripheral resistance; PRA = plasma renin activity; EP = plasma epinephrine; NEPI = plasma norepinephrine; UNaV = 24-hour urinary sodium excretion; UA = urinary aldosterone; UKV = 24-hour urinary potassium excretion, Wt = body weight; NS = not significant.

*Significant (p < 0.05 or less) change between the 150 and 10 mEq sodium intake.
pronounced after sodium depletion when the renin-angiotensin system was activated. Central venous pressure tended to decrease following teprotide during the 150 mEq sodium diet, and to increase after teprotide during the 10 mEq diet (fig. 1), but these changes were not significant. Table 1 also shows the hemodynamic and humoral responses to sodium depletion in the six normal subjects who were investigated during both diets. During sodium depletion, plasma renin activity was increased consistently in every subject (by an average of 250%) while plasma epinephrine tended to decrease (by an average of 13%), and plasma norepinephrine was inconsistently and not significantly increased by an average of 31%. When data from both studies in all subjects were analyzed, the decrease in mean arterial pressure by teprotide correlated significantly with the control plasma renin activity \( r = 0.60, p < 0.05, n = 14 \) measurements. The same degree of correlation existed between the control plasma renin activity and the decrease in total peripheral resistance by teprotide \( r = 0.60, p < 0.05, n = 14 \).

Plasma catecholamines were not affected by teprotide either during the 150 or 10 mEq sodium intake period (table 1). The magnitude of the decrease in mean arterial pressure by teprotide was not significantly related to the control plasma level of epinephrine \( r = 0.04, p: NS, n = 14 \) or of norepinephrine \( r = 0.24, p: NS, n = 14 \). Likewise, the decrease in total peripheral resistance by teprotide was not significantly related either to the control plasma epinephrine \( r = 0.19, p: NS, n = 14 \), or to the control plasma epinephrine \( r = 0.24, p: NS, n = 14 \).

**Mechanism of Fainting During Teprotide**

Following teprotide, there were five episodes of fainting, one occurring during the 150 mEq sodium intake and four during the 10 mEq sodium intake. During fainting, the mean arterial pressure was 45 ± 4 mm Hg, cardiac output 3.62 ± 0.01 liters/min, stroke volume 47 ± 4 ml/beat, total peripheral resistance 13 ± 1 units, and heart rate 67 ± 5 beats/min. When compared with values in subjects who did not faint (fig. 2), the levels of mean arterial pressure, cardiac output, and stroke volume were significantly lower during fainting, but there was no difference in either heart rate or peripheral resistance between syncopal and nonsyncopal subjects.

**Effects of Isometric Exercise**

**Before Teprotide**

During the 150 mEq sodium intake and before the administration of teprotide, hand grip increased mean arterial pressure from 74 ± 5 to 93 ± 5 mm Hg (26% ± 3%, \( p < 0.001 \)), mainly because of a concurrent increase in cardiac output from 4.44 ± 0.30 to 5.13 ± 0.46 liters/min (15% ± 5%, \( p < 0.001 \)); the concurrent 10% ± 3% increase in total peripheral resistance was not significant. Cardiac output was increased during hand grip because of an increase in heart rate from 66 ± 2 to 76 ± 3 beats/min (15% ± 4%, \( p < 0.001 \)). Stroke volume did not change significantly (fig. 3). Plasma epinephrine was increased with hand grip from 60 ± 9 to 113 ± 25 pg/ml (101% ± 37%, \( p < 0.05 \)), but norepinephrine was not affected by hand grip (282 ± 26 pg/ml before, and 285 ± 27 pg/ml during hand grip).

During the 10 mEq sodium intake, mean arterial pressure was again increased by hand grip from 68 ± 1 to 95 ± 3 mm Hg (40% ± 4%, \( p < 0.05 \)) because of a
concurrent increase in cardiac output from 3.75 ± 0.34 to 4.13 ± 0.41 liters/min (10% ± 3%, p < 0.05); there was no concurrent significant change in peripheral resistance (fig. 3). The increase in cardiac output with hand grip was again due to the increase in heart rate from 67 ± 5 to 76 ± 6 beats/min (13% ± 3%, p < 0.01).

Plasma epinephrine was not significantly increased during hand grip from 56 ± 8 to 80 ± 8 pg/ml (35% ± 25%). Plasma norepinephrine was increased from 261 ± 58 to 362 ± 100 pg/ml (35% ± 15%), but the difference was again not significant.

**After Teprotide**

During the 150 mEq phase of the study, hand grip increased the mean arterial pressure from 69 ± 4 to 88 ± 4 mm Hg (28% ± 3%, p < 0.001), again because of an increase in cardiac output from 5.05 ± 0.40 to 6.87 ± 0.72 liters/min (38% ± 16%, p < 0.025); there was no significant change in peripheral resistance (fig. 3). After teprotide, the increase in cardiac output by hand grip was due to the increase in both heart rate from 69 ± 3 to 80 ± 5 beats/min (17% ± 4%, p < 0.005) and in stroke volume from 74 ± 4 to 86 ± 5 ml/beat (18% ± 6%, p < 0.05). Plasma epinephrine (fig. 4) was significantly increased by hand grip from 91 ± 14 to 114 ± 12 pg/ml (29% ± 7%, p < 0.005), and norepinephrine from 295 ± 52 to 305 ± 48 pg/ml (29% ± 10%, p < 0.005).

During the 10 mEq sodium diet, hand grip again increased mean arterial pressure, from 54 ± 3 to 68 ± 4 mm Hg (25% ± 1%, p < 0.005), which was due to an increase in both cardiac output from 4.61 ± 0.26 to 5.07 ± 0.63 liters/min (11% ± 14%), and peripheral resistance from 12 ± 0.5 to 14.5 ± 1 units (19% ± 12%), but neither of these changes was statistically significant. The increase in cardiac output was due to an increase in heart rate from 73 ± 6 to 80 ± 7 beats/min (11% ± 5%, p < 0.05), while stroke volume did not change (63 ± 3 ml/beat) (fig. 3). Plasma epinephrine (fig. 4) was increased by hand grip from 91 ± 14 to 114 ± 12 pg/ml (29% ± 7%, p < 0.005), and norepinephrine from 295 ± 52 to 305 ± 48 pg/ml (29% ± 10%, p < 0.005).

**Hemodynamic Effects of Standing During Converting Enzyme Inhibition with Teprotide**

As can be seen from table 2, the ability to increase heart rate and peripheral resistance and therefore to sustain arterial pressure despite the decrease in cardiac output after assuming the upright posture was preserved. Therefore, arterial pressure was maintained during converting enzyme inhibition not only during
the normal sodium intake but also during the low sodium intake. Consequently, no postural hypotension was observed during standing despite the very low mean arterial pressure in the supine position.

Discussion

Hemodynamic Effects of Converting Enzyme Inhibition in Normotensive Subjects

The results of the present study show (table 1) that converting enzyme inhibition with teprotide decreases arterial pressure in normal subjects even in the sodium replete state. Our findings are in agreement with those of MacGregor et al. who have reported that another converting enzyme inhibitor, captopril, decreased arterial pressure in normotensive subjects not only during low sodium intake but also during normal or even high sodium intake, although the hypotensive response was the smallest when captopril was given during high sodium intake.

In our present study, the decrease in blood pressure after administration of the inhibitor was due to a decrease in peripheral resistance (peripheral vasodilation) during both the sodium-replete and sodium-depleted states (table 1). Similar action has also been documented in the normotensive dog, and in hypertensive subjects during low sodium intake. Furthermore, other studies have demonstrated a hypotensive effect of captopril in salt-replete dogs.

Effect of Low Sodium Intake on Plasma Catecholamines

Our results show that 10 mEq of sodium intake for 5 to 6 days does not alter plasma catecholamines (table 1) in normotensive subjects. This finding is not in agreement with those of other investigators who have reported that plasma norepinephrine increases during low sodium intake. Differences in the degree and duration of sodium and volume depletion and/or the concurrent usage of diuretics may account for this discrepancy. However, the same degree of sodium and volume depletion that failed to increase plasma catecholamines did increase plasma renin activity significantly. Moreover, in our study, low sodium intake did not appear to alter the response of catecholamines during the stress imposed by hand grip, but greater norepinephrine increments during low sodium intake have been observed by other investigators in normotensive subjects after the assumption of upright posture, which is probably a stronger stimulus than the 30% hand grip that we used.

Effect of Angiotensin II Antagonism and Inhibition on Plasma Catecholamines

It is known that angiotensin II potentiates the release of norepinephrine from the adrenomedullary nerve endings and facilitates the release of epinephrine from the adrenal gland. However, our results show that during static exercise converting enzyme inhibition with teprotide did not attenuate (block) the release of catecholamines because both were increased rather than decreased during hand grip (fig. 4). Teprotide also did not lower plasma catecholamines in subjects in the quiet seated position (table 1). In other studies, the plasma norepinephrine level was decreased during teprotide, but only following the improvement of heart failure. However, plasma catecholamine levels were similar during maximal exercise before and after saralasin administration in normotensive subjects. In yet another study, saralasin increased (but only transiently) plasma catecholamines in hypertensive patients. On the other hand, in hypertensive patients catecholamines were not decreased by captopril (SQ 14,225) in either the supine or the head-up tilt position. Actually, in this study plasma catecholamines were (as normally expected) increased during head-up tilt despite the presence of captopril. Captopril also did not affect plasma norepinephrine in sodium-depleted hypertensive or normal subjects.

These apparently conflicting results can probably be explained by the varying and occasionally contrasting effects of converting enzyme inhibition on the sympathetic nervous system. Thus, while the accumulation of angiotensin I and possibly bradykinin could stimulate directly the release of catecholamines, the decrease in the level of angiotensin II might cause the opposite effect since stimulation by angiotensin II of the nerve endings might cause the concomitant hemodynamic alterations that occur with static and dynamic exercise, with postural changes, or in heart failure, conditions that further influence catecholamine release, via the baroreflex or other mechanisms. Another complicating factor is the depression of the baroreceptor reflex and the tyramine-induced catecholamine release that occur in the low sodium state. However, it is still possible that small-to-moderate changes in norepinephrine release from the nerve endings may occur without any detectable changes in the overall plasma level. Plasma norepinephrine levels per se may not represent an ac-
Curate index of sympathetic nervous system activity, since numerous factors may affect plasma norepinephrine levels (rate of release, reuptake, metabolism, and renal clearance).

Cardiovascular Reflexes During Converting Enzyme Inhibition

In our study as well as previous studies in normal human subjects and hypertensive subjects, the expected compensatory increase in heart rate during the fall in blood pressure after SQ 20,881 administration was either minimal or virtually absent. It is possible that the gradual decrease in blood pressure and/or angiotensin II inhibition somehow modulates baroreceptor responsiveness, or angiotensin inhibition may enhance parasympathetic activity. Captopril has also been reported to affect the function of the autonomic nervous system in hypertensive patients.

Although reflex changes of heart rate are absent during converting enzyme inhibition in the supine and seated positions, our results provide evidence that baroreflex function is normal, as can be judged from the tachycardia and vasoconstriction (table 2) that occur during a short period of standing. Similar findings during short periods of head-up tilt have been reported in hypertensive patients during chronic angiotensin inhibition with the oral converting-enzyme inhibitor, captopril. However, in other studies in normal subjects and hypertensive patients, when prolonged (30-60 minutes) head-up tilt was combined with volume depletion during angiotensin inhibition, a marked decrease in blood pressure and fainting occurred, despite the increase in plasma norepinephrine and heart rate.

The findings from these latter studies suggest that a marked reduction in cardiac output via the stroke volume mechanism caused by the prolonged passive head-up tilt probably contributed to the hypotension induced by angiotensin inhibition. That this explanation is probably correct is further supported from our findings in the present study, which show that in the normal subjects who fainted in the seated position, in comparison with those who did not, not only the blood pressure but also the cardiac output was lower during the administration of teprotide. This phenomenon has also been observed in hypertensive subjects who fainted during teprotide administration (fig. 5). Nevertheless, impairment of cardiovascular reflexes during angiotensin blockade (inhibition or antagonism) has been reported in clinical and experimental studies. This impairment may contribute to fainting under certain circumstances. The lack of tachycardia despite fainting (fig. 2) may also be due to an increased vagal tone, since angiotensin II inhibition with teprotide would eliminate the vagolytic effect of the hormone.

During isometric exercise with hand grip (fig. 3), the expected normal hemodynamic response, that is, an increase in arterial pressure mediated via an increase in cardiac output because of the concurrent increase in heart rate, was preserved during both the 150 and 10 mEq sodium intakes, and during converting enzyme inhibition with teprotide. This normal response during teprotide administration contrasts with the response obtained during administration of the beta adrenergic blockers, which also interrupt the renin angiotensin system. During adrenergic beta blockade, the increase in blood pressure with hand grip is mediated via an increase in total peripheral resistance, probably caused by the unopposed alpha adrenergic tone. In the present study, however, during the 10 mEq sodium diet and teprotide the increase in arterial pressure during hand grip was partially due to an increase in peripheral resistance as well as to the increase in cardiac output (fig. 3). This vasoconstriction during isometric exercise in the presence of angiotensin II inhibition is probably due to the increased plasma catecholamines (fig. 4). The cardiovascular responses to dynamic and isometric exercise are also normal during captopril administration.

In summary, converting enzyme inhibition with teprotide decreases arterial pressure in normotensive subjects mainly during low sodium intake and to a lesser degree during normal sodium intake. Moreover,
cardiovascular responses to standing and isometric exercise remain intact during converting enzyme inhibition. These results taken together suggest that the renin-angiotensin system participates in the maintenance of arterial pressure in normotensive subjects, but does not appear to play a major role in mediating the cardiovascular responses during standing and isometric exercise when the sympathetic nervous system is intact. Finally, syncope during converting enzyme inhibition is caused by a concurrent decrease in both arterial pressure and cardiac output.

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A P Niarchos, T G Pickering and J H Laragh

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