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Plasma Norepinephrine During Stress in Essential Hypertension

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SUMMARY **Comparative studies of plasma norepinephrine in patients with essential hypertension and in normotensive controls have consistently reported higher mean *resting* levels of norepinephrine in the hypertensive groups, but the hypertensive-normotensive differences have often been small and, in about three-fifths of the studies, not statistically significant. The author reviewed the medical literature to test the hypothesis that, during stress, hypertensive-normotensive differences in norepinephrine become more apparent. Among 24 studies involving orthostatic stress, the increment in norepinephrine with standing was similar for hypertensives and normotensives (239 vs 230 pg/ml). In contrast, among eight studies involving exercise, the increment in norepinephrine was significantly greater in hypertensives (834 vs 450 pg/ml). For both standing and isotonic exercise, absolute changes in norepinephrine with stress correlated with basal norepinephrine across the hypertensive but not the normotensive groups. These results are consistent with the existence within the hypertensive population of a subgroup of patients with elevated norepinephrine levels at rest and excessive sympathetic responsiveness to stress. However, the available literature is decidedly lacking in studies about other types of stress besides standing and exercise.** (Hypertension 3: 551–556, 1981)

KEY WORDS · **norepinephrine** · **catecholamines** · **hypertension** · **stress** · **exercise** · **cold pressor test**

BECAUSE plasma norepinephrine levels seem to reflect sympathetic neural activity,[1] many studies in the last decade have used plasma norepinephrine determinations to test the hypothesis that excessive sympathetic activity occurs in essential hypertension. Comparative studies of plasma norepinephrine in patients with essential hypertension and in normotensive controls have consistently reported higher *resting* levels of norepinephrine in the hypertensive groups, but the hypertensive-normotensive differences have often been small and, in about three-fifths of the studies, not statistically significant.[2] It may be that in *nonresting* situations, hypertensive-normotensive differences become more apparent. Accordingly, this paper reviews the recent medical literature to determine whether patients with essential hypertension show exaggerated plasma norepinephrine responses to stress.

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Methods

There have been many definitions, and arguments about definitions, of stress. For the purposes of this review, a stressful stimulus is defined as one that, in the absence of a known pathological state, produces increases in sympathetic nervous system activity. Examples of stressful stimuli are orthostasis; isotonic and isometric exercise; exposure to cold; hypoglycemia, hypoxia, or pain; and environmental situations eliciting emotional responses such as anxiety or anger.

The author reviewed studies in which plasma norepinephrine responses to one or more of these stresses were compared in a group of patients with essential hypertension and in a normotensive control group. The studies satisfied these criteria: 1) they were published in English; 2) they were not abstracts, summaries of previously published data, or presentations of the same data as previously published; and 3) they used a sensitive, specific fluorimetric assay technique (such as that of Renzini et al.[3]), a radioenzymatic technique, or high pressure liquid chromatography with electrochemical detection.

To locate these studies, the author conducted several MEDLINE searches for interactions among hypertension, catecholamines, norepinephrine, stress, cold, hypoglycemia, emotions, hypoxia, and pain; and then culled additional articles by inspecting the bibliographies of the publications listed in MEDLINE.

When necessary, mean group norepinephrine values were derived from figures, or from the weighted contributions of listed subgroups. When "total catecholamines" were reported, the norepinephrine concentration was assumed to be 80% of the total. In studies using more than one intensity of stress, only data for the maximum intensity were considered.

Statistical testing used independent- and dependent-means t tests and Pearson correlation coefficients.[4]

Results

Standing

Table 1 summarizes results obtained from 24 comparative studies of plasma norepinephrine during standing in patients with essential hypertension and in normotensive controls. Basal mean norepinephrine levels were higher in the hypertensive than normotensive group in 20 of the 24 studies, with a mean hypertensive-normotensive difference of 44 pg/ml ($t = 4.28$, $p < 0.001$). During standing, the mean hypertensive-normotensive difference remained significantly different from zero (53 pg/ml, $t = 2.54$, $p < 0.05$), but with much less consistent data.

Standing did *not* significantly increase the mean hypertensive-normotensive difference in norepinephrine, and the increment in norepinephrine with standing for the hypertensives was similar to that for the normotensives (239 vs 230 pg/ml). Basal hypertensive-normotensive differences correlated strongly with hypertensive-normotensive differences during standing ($r = 0.77$, $p < 0.01$).

When expressed in percents, normotensives actually increased norepinephrine to a greater extent during standing than did hypertensives (102% vs 85%, $t = 2.54$, $p < 0.05$). For periods less than or equal to

TABLE 1. *Plasma Norepinephrine in Patients with Essential Hypertension and in Normotensives During Standing*

Reference	No. H/N	Mean age H/N	Time (min)	Assay	Basal MAP (mm Hg)	Stand MAP (mm Hg)	Basal NE (pg/ml)	Stand NE (pg/ml)
Bertel et al.[5]	24/20			Rc			260/250	505/406*
Brecht et al.[6]	59/15		7	F			257/135	498/359*
Brecht & Schoeppe[7]	87/87		7	F			201/128	405/278*
De Champlain et al.[8]	14/10		20	Rc (TC)			345/182	666/408*
DeQuattro & Chan[33]	27/25		5	Rc (TC)	117/76	119/77	283/218	418/386
Eide et al.[9]	7/7	40/36	60	F	109/89	110/92	240/167	494/529
Eng et al.[10]	20/17	47/34	5	Rc	114/90	123/102	390/250	654/405*
Franco-Morselli et al.[11]	27/12		10	Rc	103/87	124/92	252/231	472/529
Franco-Morselli et al.[12]	19/11	43/45	10	Rc	116/90		269/248	491/559
Henry et al.[13]	73/100		120	Rp	119/88		151/147	263/246
Hjemdahl & Eliasson[14]	7/7	35/35	10	LC	104/82	115/95	436/353	776/533
Jones et al.[15]	31/28	47/37	3	Rp	124/88	134/98	409/354	639/596
Kafka et al.[16]	15/18	50/50	5	Rp	112/91		265/289	497/524
Lake et al.[18]	151/117	43/35	5				297/294	509/590
Lake et al.[1]	24/44	43/35	10/5	Rp			306/287	588/538
Lake[17]	67/84	44/33	5	Rp			339/304	595/543
Lake & Ziegler[34]	56/29	46/40	5	Rp	112/89	113/87	249/253	588/673
Miura et al.[19]	60/18		60	F	120/87		189/130	364/287
Sever et al.[20]	100/48		5	Rp	121/95	124/98	352/372	628/643
Sever et al.[21]	56/59		5	Rp	124/92	126/94	411/403	737/639
Taylor et al.[22]	51/26	46/40	5	Rc	119/98	115/87	240/260	435/456
Vlachakis[23]	38/14	48/49	10	Rc			256/205	540/429
Vlachakis & Mendlowitz[24]	60/23	48/46	10	Rc	116/88	127/95	282/206	564/458*
Weidmann et al.[25]	79/90		60	R	123/89		202/169	302/344
Mean		45/40			116/89	121/92	287/243	526/473*

H = hypertensive; N = normotensive; Rc = catechol-O-methyltransferase radioenzymatic; Rp = phenylethanolamine-N-methyltransferase radioenzymatic; F = fluorimetric; LC = liquid chromotographic-electrochemical detection; TC = total catecholamines; MAP = mean arterial pressure.

*Significant hypertensive-normotensive difference during standing ($p < 0.05$.).

5 minutes of standing, the groups increased norepinephrine by a similar percentage (84% vs 78%), but for periods longer than 5 minutes, normotensives increased norepinephrine significantly more than hypertensives (121% vs 89%, $t = 2.98$, $p < 0.02$).

Six studies reported significantly higher hypertensive than normotensive norepinephrine levels during standing, as well as an increase in the hypertensive-normotensive difference. The reason for these positive results was *not* excessive mean norepinephrine levels in the hypertensives during standing, since mean standing hypertensive levels were similar in the positive and negative studies (549 vs 519 pg/ml). Rather, *normotensive control* levels during standing were significantly lower in the positive studies (386 vs 502 pg/ml, $t = 2.25$, $p < 0.05$). These findings suggest that factors in the selection, characteristics, or treatment of the normotensive control groups helped to determine that the results would be positive. One of the positive studies[10] included a normotensive control group comprised mainly of members of the laboratory staff, and this type of group is now known to have lower resting levels of norepinephrine than other normotensives.[16] The other five positive studies did not discuss the constitution of the control groups beyond mentioning that the normotensives were healthy.

Across the hypertensive groups, the absolute change in norepinephrine from baseline with standing correlated 0.64 ($p < 0.01$) with the resting norepinephrine level; in contrast, across the normotensive groups, the change in norepinephrine from baseline was unrelated to the resting level ($r = 0.25$).

These findings are consistent with the existence within the hypertensive population of a subgroup of patients with elevated norepinephrine levels at rest and excessive sympathetic responsiveness to standing. However, the lack of a significant increment in overall hypertensive-normotensive differences with standing suggests that, when considered as a single population, hypertensives do not show exaggerated plasma norepinephrine responses to this stimulus.

Exercise

Table 2 summarizes the results of studies comparing plasma norepinephrine responses to exercise in patients with essential hypertension and in normotensive controls. The eight studies reported higher mean norepinephrine levels during or after exercise in the hypertensives (by 529 pg/ml, $t = 3.46$, $p < 0.02$ overall; 761 pg/ml, $t = 4.41$, $p < 0.02$ for isotonic ex-

TABLE 2. *Plasma Norepinephrine in Patients with Essential Hypertension and in Normotensives During Exercise*

Reference	No. H/N	Mean age H/N	Type/ intensity time (min)	Basal MAP (mm Hg)	Exercise MAP (mm Hg)	Basal NE (pg/ml)	Exercise NE (pg/ml)
Bertel et al.[5]	24/20		Bicycle 75% of PCWmax			263/250	1393/1190
Philipp et al.[26]	29/29	38/33	Bicycle 200 W 2			216/173	1213/563*
Planz et al.[27]	8/8	31/30	Bicycle 150 W 5	119/97	141/115	552/240	1792/776*
Robertson et al.[28]	9/10	25/27	Treadmill 4 mph 3	101/86		510/400	1610/890*
Vlachakis & Aledort[29]	22/13	50/44	Handgrip 2/3 max 3	113/95	145/135	277/234	675/570
Vlachakis[23]	38/14	48/49	Handgrip 2/3 max 5		212/197†	265/205†	501/350*
Vlachakis & Mendlowitz[24]	37/14	47/49	Handgrip 2/3 max 5	116/88	144/117	282/206	527/351*
Watson et al.[30]	6/5	46/35	Bicycle 85% HRmax 8	130/102		938/429	2265/1050*
Mean				116/94	143/122	413/267	1267/718*

PCWmax = predicted maximum work capacity; W = watts; HRmax = maximum predicted heart rate.
*Significant hypertensive-normotensive difference during exercise ($p < 0.05$).
†Systolic pressure. Basal norepinephrine values not necessarily supine.

ercise; and 144 pg/ml, $t = 6.93$, $p < 0.025$ for isometric exercise), with an increase in the mean hypertensive-normotensive difference (from 146 to 529 pg/ml, $t = 3.66$, $p < 0.01$ overall; from 197 to 761 pg/ml, $t = 5.88$, $p < 0.02$ for isotonic exercise; and from 60 to 144 pg/ml, $t = 7.36$, $p < 0.02$ for isometric exercise) when compared with the basal condition. The increment in norepinephrine with exercise among the hypertensives also was significantly greater than the increment among the normotensives (834 vs 450 pg/ml, $t = 3.66$, $p < 0.01$ overall; 1159 vs 595 pg/ml, $t = 5.88$, $p < 0.005$ for isotonic exercise; and 293 vs 209 pg/ml, $t = 7.36$, $p < 0.02$ for isometric exercise). Increments in norepinephrine were greater with isotonic than isometric exercise (877 vs 251 pg/ml overall, $t = 6.79$, $p < 0.001$), despite seemingly severe handgrip exercise as an isometric stress.

When expressed in percents, the hypertensive groups increased norepinephrine in response to exercise to a greater extent than the normotensive groups in seven of the eight studies (224% vs 172%). This difference was not, however, statistically significant ($t = 1.81$), at least partly due to unusually high basal norepinephrine levels and hypertensive-normotensive differences in a few of the studies.

As with orthostatic stress, hypertensive-normotensive differences during exercise correlated significantly with hypertensive-normotensive differences at rest ($r = 0.86$, $p < 0.01$). Further, for isotonic exercise, the absolute change in norepinephrine from baseline correlated significantly with the baseline level across the hypertensive groups ($r = 0.88$, $p < 0.05$) but not across the normotensive groups ($r = 0.06$).

Since resting norepinephrine levels as well as increments in norepinephrine with stress increase with age,[32] poor age matching could have produced greater hypertensive-normotensive differences during exercise than at rest. However, in four of the studies, the groups were age-matched, with positive results still obtained.

Other Stresses

Only one study compared plasma catecholamine responses to the cold pressor test in hypertensives and normotensives,[31] and this study used measurement of total catecholamines rather than norepinephrine alone. The level of plasma catecholamines during the test was significantly higher in the hypertensives than the normotensives (619 vs 467 pg/ml), with an increase in the mean hypertensive-normotensive difference from 61 to 152 pg/ml.

Similarly, only one study has compared hypertensive and normotensive responses to psychological stress, in this case, a color-word conflict test.[14] The stress increased norepinephrine only slightly in both hypertensives (436 to 479 pg/ml) and normotensives (353 to 369 pg/ml), with an increase in the hypertensive-normotensive difference from 83 to 110 pg/ml.

No studies have compared plasma norepinephrine responses of hypertensives and normotensives to hypoxia, hypoglycemia, or pain.

Discussion

Of the several stresses known to stimulate the sympathetic nervous system, only orthostasis and exercise have been extensively studied. Increments in norepinephrine to standing were found to be similar in hypertensives and normotensives. In contrast, hypertensives showed much larger increments in norepinephrine in response to exercise than normotensives, resulting in large hypertensive-normotensive differences, averaging 529 pg/ml, during this stress. For both standing and isotonic exercise, the absolute change in norepinephrine from baseline correlated positively with the baseline level for the hypertensive but not normotensive group.

Why should there have been such a difference between the results obtained during standing and those obtained in response to exercise? The simplest explanation is that orthostasis is not as potent a stimulus for norepinephrine release as is exercise. A prediction from this is that the extent of the hypertensive-normotensive differences in norepinephrine should vary with the intensity of the stress. In the two studies that used graded levels of exercise, the hypertensive-normotensive differences in norepinephrine did, in fact, increase progressively from the resting to orthostatic positions, and then across the several intensities of exercise.

An alternative explanation for the discrepancy between the results obtained with standing and with exercise is that only relatively younger subjects would be exercised severely, and it has previously been shown that hypertensive-normotensive differences in norepinephrine vary inversely with age.[3] The mean age of the subjects undergoing orthostatic stress was in fact greater than that of the subjects undergoing isotonic exercise (42 vs 34 years), but the difference did not attain statistical significance. In the one study in which norepinephrine responses to isotonic exercise were analyzed separately by age group, hypertensive-normotensive differences in response to exercise increased with the age of the group studied.[5]

Unfortunately, little comparative data are available about hypertensive-normotensive differences in norepinephrine in response to stresses other than orthostasis and exercise. Conclusions about the relationship between hypertensive-normotensive differences and intensity of stress must be tempered, therefore, by the possibility that exercise differentiates hypertensive and normotensive groups for reasons specific to exercise. For instance, if hypertensives were simply less physically trained, one might predict that they would show greater norepinephrine responses to exercise — especially submaximal isotonic exercise — than to other stresses.

The available exercise data have been difficult to analyze because of variability from study to study in the type, intensity, and duration of exercise; testing of only poorly described — and possibly biased — subgroups from among the hypertensives and normotensives; poor age matching, in a situation where both resting and stress-related increments in norepinephrine are known to vary with age; small group sizes;

and reporting total catecholamine levels, where the relative contributions of norepinephrine and epinephrine to the total may change during the testing.

A rather surprising finding, derived both from studies of orthostatic stress and of isotonic exercise, was that absolute changes in norepinephrine from baseline during stress correlated with baseline norepinephrine levels across the hypertensive *but not the normotensive* groups. This finding is consistent with the hypothesis that, among the hypertensive population, there exists a subgroup of patients with elevated basal norepinephrine levels and excessive sympathetic responsiveness to stress; while among the normotensive population, variations in basal norepinephrine represent sampling error of no physiological significance. Eng et al.[10] have recently demonstrated that "high norepinephrine" hypertensives do show greater norepinephrine responses to standing than "normal norepinephrine" hypertensives. Unfortunately, their data do not include the norepinephrine responses of the normotensives with relatively high or low basal norepinephrine.

Because the hypertensive groups have often shown higher basal norepinephrine levels than the normotensive groups, data analyses based on absolute changes from baseline yielded entirely different results from analyses based on percent changes. At the current state of knowledge in the area, it is impossible to state with confidence which type of analysis makes more physiologic sense.

In summary, review of the available medical literature about the relationship between stress and sympathetic activity in essential hypertension has resulted in these conclusions:

Resting plasma norepinephrine levels are usually greater in hypertensive than normotensive groups, although often not significantly so.

Standing does not significantly increase hypertensive-normotensive differences in norepinephrine.

Exercise — particularly isotonic exercise — does significantly increase the mean hypertensive-normotensive difference.

For both standing and isotonic exercise, absolute changes in plasma norepinephrine from baseline correlate with baseline levels across hypertensive but not normotensive groups.

There is inadequate or no published information about the effects or other stresses besides standing and exercise on plasma norepinephrine in essential hypertension.

These findings are consistent with the following hypotheses:

1. The extent of hypertensive-normotensive differences in sympathetic activity depends on the intensity of stress.

2. Overall, patients with essential hypertension show excessive sympathetic neural responses to exercise.

3. A subgroup within the hypertensive population shows excessive plasma norepinephrine at rest and accentuated sympathetic responses to stress.

Further testing of patients with essential hypertension who show elevated norepinephrine levels at rest should include measurement of these patients' norepinephrine responses to several stresses, to test the hypothesis that sympathetic neural activity at rest and reactivity to stress are abnormal in a proportion of patients with essential hypertension.

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