Plasma Catecholamines and Essential Hypertension

An Analytical Review

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SUMMARY **Of 78 comparative studies of plasma catecholamines in patients with essential hypertension and in normotensive controls, most reported higher catecholamine levels in the hypertensives, although only about 40% of the studies were positive (reporting statistically significant hypertensive-normotensive differences). Although there was dramatic variability in catecholamine values within and across studies, virtually all studies of norepinephrine in *young, consistently hypertensive* patients were positive. The likelihood that a study was positive with respect to norepinephrine was independent of the likelihood with respect to epinephrine, so that total catecholamine values, or else the sum of norepinephrine plus epinephrine, differentiated hypertensives from normotensives to a greater extent than levels of either substance alone. The preponderance of literature on the subject supports the hypothesis that increased plasma catecholamine concentrations occur in some patients with essential hypertension. Elevated plasma norepinephrine in relatively young, established hypertensive patients is consistent with a pathophysiologic role for increased sympathetic neural activity in this subgroup. (Hypertension 5: 86–99, 1983)**

KEY WORDS • **hypertension** • **norepinephrine** • **epinephrine** • **catecholamines** • **blood pressure** • **sympathetic nervous system**

THE possible pathophysiologic role of excessive sympathetic nervous system activity in essential hypertension has aroused persistent interest and controversy. More than 75 studies have compared levels of norepinephrine (NE), the neurotransmitter of the sympathetic nervous system, or epinephrine (E), secreted by the adrenal medulla, in patients with essential hypertension and in normotensive controls.[1–78] No consensus has emerged about whether patients with essential hypertension show abnormal sympathetic neural or sympathoadrenomedullary activity as indicated by plasma catecholamine levels.

The problem is quite complex, for at least three reasons. First, plasma catecholamines are difficult to measure. The assay techniques can be tedious and capricious; the concentrations of NE and especially of E are extremely small, averaging about 250 and 50 pg/ml respectively; and blood samples have to be handled carefully to avoid oxidation of the catecholamines.

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Second, NE levels vary with a wide variety of common and often difficult to control environmental factors, including psychological stress,[79] familiarity with the medical environment,[42] caffeine,[80] and sodium intake.[80] Therefore, differences in methods of patient selection, patient characteristics, and treatment can lead to entirely different findings.

Third, venous plasma catecholamine levels represent the product not only of sympathetic and sympathoadrenomedullary secretion but also reuptake by nerve endings, metabolic degradation, uptake into non-neural tissue, binding to postsynaptic receptors, the site of sampling, and diffusion between the synaptic cleft and the general circulation.

Analysis of the extensive literature on this subject clearly shows a few consistencies, however, so that some conclusions can be drawn. This review summarizes the literature on plasma catecholamine levels in essential hypertension and identifies factors characterizing studies reporting statistically significant hypertensive-normotensive (H-N) differences in plasma catecholamines. Knowledge of the factors that distinguish positive from negative studies should explain the disparate results already published and help investigators conduct future studies.

This analysis updates, extends, and refines a previous one that was based on 32 studies of NE[81] alone and did not consider plasma E, dopamine (DA), or total catecholamines (TC). Since then, an additional 32 studies of NE have been completed, allowing consideration of factors that could not be analyzed in the previous review. In addition, 31 studies of E, six of DA, and 12 of TC have been analyzed separately in the current review.

Methods

To locate the reviewed studies, I conducted MEDLINE searches for interactions among NE, E, catecholamines, and hypertension, and then culled additional articles using the bibliographies of the listed publications.

The reviewed studies satisfied these criteria: 1) they were published as journal articles in English since 1970; 2) they included both a group of patients with essential hypertension and a normotensive control group; 3) they reported plasma NE, E, DA, or TC in resting, supine individuals; and 4) they used a sensitive and specific assay technique, either a radioenzymatic (R) procedure, a modern fluorimetric (F) method such as that of Renzini et al.,[82] or high pressure liquid chromatography with electrochemical detection.[83] Abstracts and obvious duplications were excluded.

The large number of published studies allowed a statistical approach in which each study provided single data points for the hypertensive and normotensive groups, with comparisons conducted across studies for factors of interest.

When necessary, mean group catecholamine values were derived from figures, or from the weighted contributions of listed subgroups; and group standard deviations (SD) were calculated from the standard errors of the mean (SEM) by multiplying the SEM by the square root of the number of observations. Statistical testing used independent- and dependent-means *t* tests, Pearson correlation coefficients, and chi-squared analyses.[84] In one case, results from two separate publications[27, 28] were grouped together because only then was an entire hypertensive group represented, as opposed to subgroups based on renin profiling.

Results

Norepinephrine

Table 1 displays summary statistics about hypertensive and normotensive mean NE levels from 64 studies. Data from the individual studies are tabulated by assay type in table 2. Of the 64 studies, 52 (81%) reported higher levels in the hypertensives, by an average of 55 pg/ml ($t = 6.75$, $p < 0.001$). In view of the pronounced interindividual variabilty of NE levels, such a small mean H-N difference could easily not have been statistically significant in many studies. And, in fact, only 25 (39%) of the 64 studies were positive with respect to NE. Since about two-fifths of the studies were positive and about three-fifths were negative, one can appreciate that any generalizations from the literature might be questioned.

If there were a variably represented "hypernoradrenergic" subgroup of hypertensives, then studies with a preponderance of these patients should have been positive due to the excessive mean NE levels in the hypertensive groups. Across the 64 studies, the mean hypertensive NE level of the positive studies was in fact higher than that of the negative studies (307 vs 258 pg/ml, $t = 2.16$, $p < 0.05$).

A preponderance of hypernoradrenergic hypertensives in positive studies would mean that the positive

TABLE 1. *Summary Data for Comparative Studies of Plasma Catecholamines in Patients with Essential Hypertension and in Normotensive Controls*

Variable	H	N	SD_H	SD_N	n	*t*	*p*
NE, F	200	146	95	45	11	6.05	0.001
NE, COMT	289	227	142	119	34	4.74	0.001
NE, PNMT	302	260	162	142	18	2.90	0.01
NE, HPLC	436	353	156	94	1	—	—
NE, R combined	294	239	150	128	52	5.55	0.001
NE, all studies	280	225	140	113	64	6.75	0.001
TC	390	255	172	72	12	4.50	0.001
E	56	43	45	38	31	3.53	0.01
DA	71	65	63	45	6	1.09	ns

H = hypertensive groups; N = normotensive groups; SD = average group standard deviation; *t* = dependent-means *t* value; NE = norepinephrine; E = epinephrine; DA = dopamine; TC = total catecholamines; R = radioenzymatic; COMT = catechol-O-methyltransferase radioenzymatic; PNMT = phenylethanolamine-N-methyltransferase radioenzymatic; HPLC = high pressure liquid chromatography with electrochemical detection; *p* = probability of statistical significance for the hypertensive-normotensive mean difference in catecholamine concentrations. All mean values expressed in pg/ml.

TABLE 2. *Plasma Norepinephrine in Resting, Supine Patients with Essential Hypertension (H) and in Normotensive Controls (N) as Determined by Various Assay Techniques*

First author (ref)	H/N (no.)	Age H/N (yrs)	MAP H/N (mm Hg)	HR H/N (bpm)	NE H/N (pg/ml)	SD H/N (pg/ml)
Fluorimetric assay						
Brecht (6)	59/15	—	—	—	257/135*	147/59
Brecht (7)	125/107	40/42	—	—	201/128*	—
Corea (11)	19/7	38/34	128/85	78/67*	172/147	96/32
DeQuattro (19)	11/12	—	—	—	157/148	99/45
Eide (22)	28/12	38/—	—	67/—	193/148*	101/45
Eide (23)	7/7	40/36	109/89	73/73	240/167*	99/31
Esler (27,28)	48/20	—	109/88	62/60	175/136	65/44
Esler (29)	21/11	—	—	—	193/138*	77/36
Miura (61)	120/30	35/30	112/87	70/69	188/130*	88/60
Miura (62)	120/49	35/33	112/83	71/70	209/160*	103/50
Philipp (67)	29/29	38/33	—	—	216/173*	72/45
Catechol-O-methyltransferase radioenzymatic assay technique						
Amann (1)	20/16	48/48	120/80	73/63*	296/322	107/112
Beretta-Piccoli (2)	34/25	39/41	109/88	67/66	238/230	115/86
Beretta-Piccoli (3)	45/26	43/39	116/89	69/63	262/221	138/94
Bertel (4)	24/20	—	—	67/62	263/250	98/121
Bolli (5)	18/15	47/49	118/83	72/60*	289/279	100/79
DeChamplain (17)	67/36	34/29	106/86	75/64*	220/169*	—
Eng (24)	20/17	47/34	114/90	85/—	390/250*	175/62
Esler (26)	41/24	37/34	—	—	323/196*	118/71
Franco-Morselli (31)	27/12	—	104/87	80/70*	277/250	286/364
Franco-Morselli (32)	19/11	43/45	116/90	82/71*	269/248	122/186
Fujiki (33)	56/33	53/47	—	—	276/242	119/120
Geffen (34)	20/8	—	—	—	400/160*	223/113
Grimm (35)	35/28	41/42	116/91	68/62*	220/220	90/80
Henquet (36)	25/25	—	108/89	73/63*	409/370	254/254
Ibsen (41)	33/31	40/40	115/91	72/64*	170/180	—
Kiowski (44)	45/34	43/43	—	68/62*	289/282	113/177
Kjeldsen (45)	20/19	51/52	135/99	—	549/357*	234/111
Kobayashi (46)	27/21	42/42	111/81	—	292/224*	94/128
Kolloch (47)	7/9	29/31	109/—	—	410/235*	108/111
Kolloch (48)	7/6	26/—	—	—	404/234*	111/78
Louis (56)	24/7	—	—	—	390/160*	—
Louis (57)	28/14	—	—	—	400/200*	212/224
Meier (58)	24/22	35/37	106/88	65/63	201/212	83/84
Messerli (59)	72/38	—	94/86	70/68	277/289	223/165
Millar (60)	8/14	—	—	—	161/135	134/91
Miura (63)	34/25	—	—	—	245/133*	140/72
Pedersen (66)	19/32	41/40	142/97	—	242/254	—
Robertson (69)	9/10	25/27	101/86	—	226/196	—
Schiffl (70)	39/37	42/40	116/90	69/63*	240/225	124/102
Skrabal (73)	69/19	38/40	134/110	—	190/190	100/60
Vlachakis (75)	38/14	48/49	119/92	76/74	256/205	139/60
Vlachakis (76)	22/13	50/44	—	—	277/234	89/90
Vlachakis (77)	60/23	48/46	116/88	—	282/206*	155/72
Weidmann (78)	79/90	46/37	123/89	—	202/169	128/91

Continued

TABLE 2. *(Continued)*

First author (ref)	H/N (no.)	Age H/N (yrs)	MAP H/N (mm Hg)	HR H/N (bpm)	NE H/N (pg/ml)	SD H/N (pg/ml)
Phenylethanolamine-N-methyltransferase radioenzymatic assay technique						
Cousineau (12)	46/28	41/39	114/89	87/75*	332/226*	198/106
DeLeeuw (18)	69/22	45/41	120/95	——	270/240	150/100
FitzGerald (30)	5/5	45/45	124/91	71/62*	350/130*	179/157
Henry (37)	32/93	41/27	119/88	——	151/144	107/105
Hofman (39)	18/18	19/18	97/90	76/72	351/248*	110/123
Hofman (40)	41/41	16/16	97/82	73/74	336/281*	146/126
Jones (42)	31/28	47/38	——	82/73*	410/354	223/160
Kafka (43)	15/18	50/50	112/91	76/61*	265/289	194/136
Lake (51)	151/117	43/45	112/88	——	297/294	143/159
Lake (52)	11/9	48/44	115/87	70/70	222/172	129/120
Lake (53)	56/29	46/40	112/89	73/62*	249/253	120/129
Lake (54)	67/84	44/33	112/86	——	339/304	188/183
Lake (55)	24/44	43/35	——	——	306/287	127/146
Ogawa (64)	81/66	48/52	——	——	250/230	180/162
Parfrey (65)	16/8	36/31	113/80	70/66	296/191*	111/31
Sever (71)	56/44	46/46	124/92	——	411/403	197/184
Sever (72)	100/48	45/47	121/95	76/72	352/372	178/171
Taylor (74)	51/26	46/40	123/89	73/76	240/260	230/257

*Statistically significant hypertensive-normotensive difference in heart rate or norepinephrine, with $p < 0.05$.

studies would also have a larger hypertensive SD than normotensive SD, while the negative studies would have a hypertensive and normotensive SD that was about equal. Overall, the ratio of hypertensive to normotensive SD *was* larger in the positive studies (1.82 vs 1.28, $t = 3.23$, $p < 0.01$).

If selection or treatment factors resulted in relatively low control group mean NE levels in some studies, those studies would have tended to be positive. Normotensive control NE levels indeed were lower in the positive studies (191 vs 246 pg/ml, $t = 3.33$, $p < 0.01$).

Finally, if studies differed in the extent of control over environmental factors, then the more carefully controlled studies should have been positive due to a lower SD across individuals. The average SD of normotensive NE levels was in fact smaller in the positive studies (87 vs 129 pg/ml, $t = 2.58$, $p < 0.05$).

Study Size

Of 29 studies with less than 50 subjects, 14 (48%) were positive, and of 35 with 50 or more subjects, 11 (31%) were positive — a nonsignificant difference in proportions. The average SD of the NE values was also similar in the two types of study size. The size of the study was therefore unrelated to the likelihood of obtaining positive results.

Type of Assay

In contrast, hypertensive and normotensive group NE levels, and the likelihood of obtaining positive results, were related to the type of assay technique used. Of 11 studies using a fluorimetric (F) assay technique, eight (73%) were positive, while only 17 of 35 (33%) using a radioenzymatic (R) assay technique were positive ($\chi^2 = 4.40$, $p < 0.05$). The average NE level was significantly higher in the R than F studies for both hypertensive (294 vs 200 pg/ml, $t = 3.86$, $p < 0.001$) and normotensive (239 vs 146 pg/ml, $t = 4.77$, $p < 0.001$) groups. The mean H-N differences, though, were virtually identical in the F (54 pg/ml) and R (55 pg/ml) studies. The average SD of NE levels was significantly greater in the R studies for both hypertensive (150 vs 95 pg/ml, $t = 3.39$, $p < 0.01$) and especially for normotensive (128 vs 45 pg/ml, $t = 4.29$, $p < 0.001$) groups.

Because positive studies were weighted disproportionately by the results derived from fluorimetric assay techniques, positive and negative studies were compared *within* assay techniques. Among F studies, mean hypertensive NE levels were higher in positive than negative studies (212 vs 168 pg/ml, $t = 2.93$, $p < 0.05$). Among R studies, the same finding occurred: mean hypertensive NE levels were higher in the positive studies (351 vs 261 pg/ml, $t = 4.27$, $p < 0.001$),

especially among studies using the catechol-O-methyltransferase (COMT) radioenzymatic assay technique, where the mean hypertensive NE level was 359 pg/ml in the positive studies and 251 pg/ml in the negative ($t = 4.39$, $p < 0.001$). Thus, when analyzed separately within assay types, the data were consistent with the presence of some hypernoradrenergic patients among the population of hypertensives.

The age of the hypertensive patients differentiated the F and R studies. All seven F studies listing the hypertensives' mean age reported a mean age less than or equal to 40 years old; while among 43 R studies, only 11 reported a mean hypertensive age less than or equal to 40 years ($\chi^2 = 10.85$, $p < 0.01$). Inclusion of relatively young hypertensives appears to have contributed to the high frequency of positive results associated with the F type of assay.

Given the relatively small H-N differences in NE, it should not be surprising that those studies reporting a large SD as a percent of the group mean tended to be negative. When the SD was expressed as a percent of the mean for the hypertensive and normotensive groups, among hypertensives the proportion of F studies where the SD was less than 50% of the mean did not differ from the corresponding proportion of R studies (60% for F, 49% for R). However, among *normotensives*, eight of 10 (80%) F studies reported an SD less than 40% of the mean, while only 13 of 47 (28%) R studies did so ($\chi^2 = 7.35$, $p < 0.01$). Radioenzymatic studies, therefore, reported higher standard deviations of normotensive norepinephrine levels when expressed as a percent of the mean.

Patient Age

Across the 51 studies that listed patient ages, the hypertensive groups were slighty but consistently older, by an average of 2.6 years ($t = 4.50$, $p < 0.001$). Mean group age correlated significantly with mean plasma NE across the normotensive but *not* the hypertensive groups ($r = 0.29$, $p < 0.05$, and $r = 0.01$, $p =$ ns).

An artifactual effect of poor age matching would require that positive studies include hypertensives who were older than normotensives, and negative studies include groups of similar age. The correlation between the difference in group mean ages and the difference in group mean NE levels, however, was nil. Further, in view of the small or absent slopes of the regression lines relating NE with age (7.7 pg/yr in normotensives, 0.4 pg/yr in hypertensives), only a grossly large age mismatch would produce the obtained average H-N difference in norepinephrine; the average actual age mismatch was too small to do so. Hypertensive-normotensive differences in positive studies did not, therefore, derive from the artifactual effects of poor age matching.

Since plasma NE increased with age across the normotensive but not hypertensive groups, one would predict that positive results would tend to occur in studies of relatively younger patients. This was exactly the case. When the hypertensive group mean age was less than 30 years, four of five (80%) studies were positive; when it was 30 to 39 years, seven of 11 (64%) were positive; 40 to 49 years, seven of 30 (23%) were positive; and 50 years or more, one of four (25%) was positive. Figure 1 shows that in studies where both the hypertensive and normotensive groups averaged 40 years old or less, the hypertensives virtually always showed higher plasma NE ($t = 5.07$, $p < 0.001$), while in studies where both groups averaged more than 40 years, H-N differences were smaller and less consistent, because the normotensives showed increased NE with age ($t = 3.09$, $p < 0.01$). Further, the data from six otherwise negative studies[4, 31, 32, 64, 71, 72] indicated statistically significant H-N differences in NE

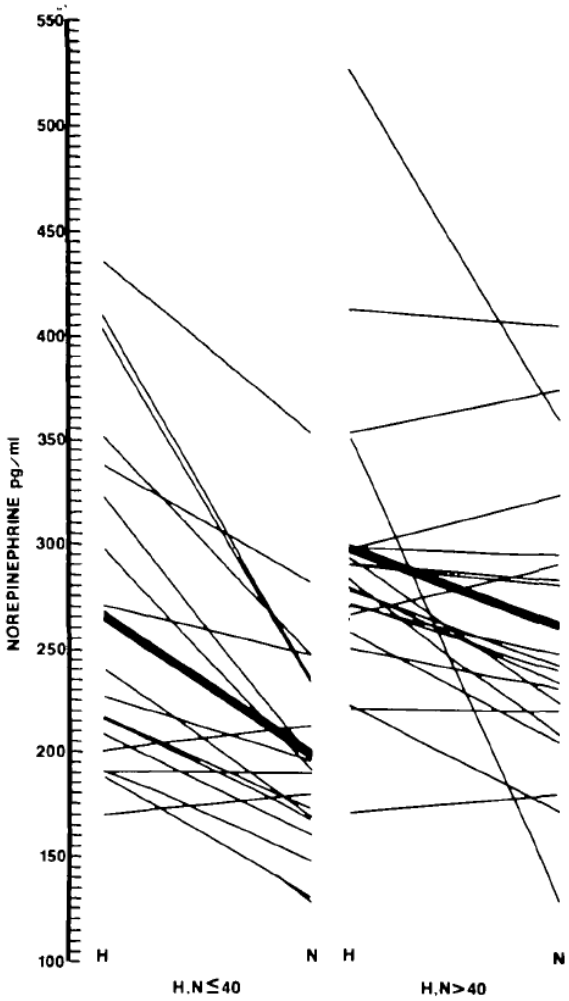

FIGURE 1. *Mean group plasma norepinephrine values in hypertensive (H) and normotensive (N) groups. Left: Hypertensives and normotensives averaging 40 years old or less. Right: Averaging more than 40 years old. Note consistently higher plasma norepinephrine in the younger hypertensives, and the increase in norepinephrine with age in the normotensives. Broad bar shows the overall group means.*

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