Plasma Norepinephrine in Essential Hypertension
A Study of the Studies

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SUMMARY Of 32 studies comparing plasma norepinephrine concentrations in hypertensive and normoten-
sive groups, 28 (88%) reported higher levels in the hypertensive group. However, only 13 (41%) of the studies
reported statistically significant hypertensive-normotensive differences in norepinephrine, leading the present
attempt to identify factors differentiating “positive” studies (those reporting significant hypertensive-
normotensive differences) from “negative” studies (those reporting nonsignificant differences). Hypertensive
norepinephrine levels were similar in positive and negative studies (281 vs 288 pg/ml), but normotensive levels
were lower in the positive studies (177 vs 269 pg/ml). When compared with the fluorimetric technique, the
radioenzymatic type of assay was associated both with a lower frequency of positive results (25% vs 100%) and
greater intrastudy standard deviations (152 vs 72 pg/ml). Hypertensive-normotensive differences varied in-
versely with age (r = -0.37). Resolution of the persisting controversy about norepinephrine levels in essential
hypertension will require more attention to the causes of variability associated with the assay technique, to
the sources, characteristics, and treatment of the normotensive controls, and to the age of the patient population.

(Hypertension 3: 48-52, 1981)

KEY WORDS • norepinephrine • catecholamines • hypertension

THE introduction about a decade ago of sensi-
tive techniques for measuring plasma norepi-
nephrine,\textsuperscript{1,2} and indications that those levels reflect sympathetic neural activity,\textsuperscript{3} promised to help
answer a perennial question in hypertension research: Does sympathetic hyperactivity cause essential hyper-
tension? Despite the subsequent publication of more
than 30 comparative studies in hypertensives and nor-
motensive controls,\textsuperscript{3-7} controversy persists about
whether patients with hypertension exhibit elevated
levels of norepinephrine. This report reexamines these
studies in an attempt to identify the causes of the in-
consistencies in results.

Methods

The studies considered in this review satisfied the
following criteria: 1) they were published since 1973,
in English; 2) they were not merely abstracts, but were
primary data sources independent of data from other
sources; 3) they specifically involved plasma
norepinephrine, not total catecholamines; 4) they used
a sensitive and reliable fluorimetric technique, such
as that of Renzini, et al.;\textsuperscript{1} a radioenzymatic assay; or
high-pressure liquid chromatography with elec-
trochemical detection; and 5) they reported resting,
supine plasma norepinephrine levels in both a nor-
motensive control group and an entire hypertensive
group (as opposed to a subgroup selected for certain
characteristics).

The large number of studies culled using these
criteria — 32 — allowed a statistical approach in
which the mean hypertensive and normotensive values
from each study provided single data points. When
mean group values had not been reported, they were
derived from the weighted contributions of the sub-
groups in the study; and when standard deviations
(sds) had not been reported, they were calculated from
standard errors of the mean (sems) by multiplying the
sems by the square root of the number of observations.
Statistical analyses used two-tailed independent-
means and dependent-means t tests, chi-squared tests,
and Pearson correlation coefficients.\textsuperscript{8} All studies,
despite their probably variable reliability, were ac-
corded equal weight.
Results

Table 1 displays hypertensive and normotensive mean norepinephrine levels from the 32 studies. Twenty-eight (88%) reported higher levels in the hypertensives, by an average of 54 pg/ml ($t = 4.06, p < 0.001$). Only 13 reported statistically significant hypertensive-normotensive differences in norepinephrine. Since about two-fifths of the studies were “positive” (i.e., reporting a significant hypertensive-normotensive difference) and about three-fifths were “negative” (reporting no significant difference), one can appreciate that any generalizations from the literature might be questioned.

What made the “positive” studies positive, and the “negative” negative? If the cause were a variably represented “hyperadrenergic” subgroup of hypertensives, then studies with a preponderance of these patients should have been positive due to the excessive mean norepinephrine levels in the hypertensive groups. However, mean hypertensive levels were not significantly higher in the positive than the negative

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Table 1. Plasma Norepinephrine Levels in Patients with Essential Hypertension (H) and in Normotensive Controls (N)

<table>
<thead>
<tr>
<th>Author</th>
<th>H/N (no.)</th>
<th>Age H/N (yrs)</th>
<th>Assay</th>
<th>MAP H/N (mm Hg)</th>
<th>NE H/N</th>
<th>SD H/N</th>
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<tbody>
<tr>
<td>Bertel et al.</td>
<td>24/20</td>
<td>41/40</td>
<td>R</td>
<td>112/93</td>
<td>263/250</td>
<td>98/121</td>
</tr>
<tr>
<td>Brecht et al.</td>
<td>59/15</td>
<td>?</td>
<td>F</td>
<td>?</td>
<td>257/135*</td>
<td>147/59</td>
</tr>
<tr>
<td>Brecht and Schoeppe</td>
<td>125/107</td>
<td>40/42</td>
<td>F</td>
<td>?</td>
<td>201/128*</td>
<td>?</td>
</tr>
<tr>
<td>Cousineau et al.</td>
<td>46/28</td>
<td>41/39</td>
<td>R</td>
<td>?</td>
<td>332/226*</td>
<td>198/106</td>
</tr>
<tr>
<td>DeLeeuw et al.</td>
<td>69/22</td>
<td>45/41</td>
<td>R</td>
<td>120/95</td>
<td>270/240</td>
<td>150/100</td>
</tr>
<tr>
<td>Eide et al.</td>
<td>7/7</td>
<td>40/36</td>
<td>F</td>
<td>109/89</td>
<td>240/167*</td>
<td>99/31</td>
</tr>
<tr>
<td>Eng et al.</td>
<td>20/17</td>
<td>47/34</td>
<td>R</td>
<td>114/90</td>
<td>390/250*</td>
<td>175/62</td>
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<tr>
<td>Esler et al.</td>
<td>21/11</td>
<td>?</td>
<td>F</td>
<td>?</td>
<td>193/138*</td>
<td>77/36</td>
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<tr>
<td>Franco-Morselli et al.</td>
<td>19/11</td>
<td>43/45</td>
<td>R</td>
<td>116/90</td>
<td>269/248</td>
<td>122/186</td>
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<td>Franco-Morselli et al.</td>
<td>27/12</td>
<td>?</td>
<td>R</td>
<td>104/87</td>
<td>277/250*</td>
<td>286/364*</td>
</tr>
<tr>
<td>Geffen et al.</td>
<td>20/8</td>
<td>?</td>
<td>R</td>
<td>?</td>
<td>400/160*</td>
<td>223/113</td>
</tr>
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<td>Henry et al.</td>
<td>32/93</td>
<td>41/27</td>
<td>R</td>
<td>119/88</td>
<td>151/144</td>
<td>107/105</td>
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<td>Hjemdahl and Eliasson</td>
<td>7/7</td>
<td>35/35</td>
<td>H</td>
<td>101/87†</td>
<td>436/353</td>
<td>156/94</td>
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<td>18/18</td>
<td>19/18</td>
<td>R</td>
<td>97/90</td>
<td>351/248*</td>
<td>110/123</td>
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<td>47/38</td>
<td>R</td>
<td>?</td>
<td>410/364</td>
<td>223/160</td>
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<td>50/50</td>
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<td>Kiowski et al.</td>
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<td>43/43</td>
<td>R</td>
<td>?</td>
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<td>98/115</td>
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<td>Kobayashi et al.</td>
<td>27/21</td>
<td>42/42</td>
<td>R</td>
<td>111/81</td>
<td>291/224*</td>
<td>94/128</td>
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<td>Lake et al.</td>
<td>67/84</td>
<td>44/33</td>
<td>R</td>
<td>112/86</td>
<td>339/304</td>
<td>188/183</td>
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<td>Lake</td>
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<td>43/45</td>
<td>R</td>
<td>112/88</td>
<td>297/294</td>
<td>143/159</td>
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<tr>
<td>Louis et al.</td>
<td>24/7</td>
<td>?</td>
<td>R</td>
<td>?</td>
<td>390/160*</td>
<td>?</td>
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<tr>
<td>Miura et al.</td>
<td>120/30</td>
<td>35/30‡</td>
<td>F</td>
<td>112/87</td>
<td>188/130*</td>
<td>88/60</td>
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<td>120/49</td>
<td>35/33</td>
<td>F</td>
<td>112/83</td>
<td>209/160*</td>
<td>?</td>
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<tr>
<td>Pedersen and Christensen</td>
<td>19/32</td>
<td>41/40</td>
<td>R</td>
<td>142/97</td>
<td>242/254</td>
<td>?</td>
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<tr>
<td>Philipp et al.</td>
<td>29/29</td>
<td>38/33</td>
<td>F</td>
<td>?</td>
<td>216/173*</td>
<td>72/45</td>
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<td>Robertson et al.</td>
<td>9/10</td>
<td>25/27</td>
<td>R</td>
<td>101/86</td>
<td>226/196</td>
<td>?</td>
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<tr>
<td>Sever et al.</td>
<td>56/59</td>
<td>46/46</td>
<td>R</td>
<td>124/92</td>
<td>411/403</td>
<td>197/184</td>
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<td>Sever et al.</td>
<td>100/48</td>
<td>45/47</td>
<td>R</td>
<td>121/95</td>
<td>352/372</td>
<td>178/171</td>
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<td>Taylor et al.</td>
<td>51/26</td>
<td>46/40</td>
<td>R</td>
<td>123/89</td>
<td>240/260†</td>
<td>230/257†</td>
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<td>Vlachakis</td>
<td>38/14</td>
<td>48/49</td>
<td>R</td>
<td>119/92†</td>
<td>256/205</td>
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<td>Vlachakis and Aledort</td>
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<td>89/90</td>
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<td>Weidmann et al.</td>
<td>79/90</td>
<td>46/37</td>
<td>R</td>
<td>123/89</td>
<td>202/169</td>
<td>128/91</td>
</tr>
</tbody>
</table>

Average/Sum 1496/1085 41/38* 114/89* 285/231* 148/124

*Significant hypertensive-normotensive difference with $p < 0.05$.
†Taken from figure.
‡Approximate ages.
R = radioenzymatic; F = fluorimetric; H = high-pressure liquid chromatography with electrochemical detection; MAP = group mean blood pressure; NE = group mean norepinephrine level; SD = standard deviation.
studies (281 vs 288 pg/ml). In contrast, the normoten-
sive control levels were significantly lower in the
positive studies (177 vs 269 pg/ml, t = 4.27, p <
0.001). Standard deviations of normotensive levels
were also smaller in the positive studies (76 vs 152
pg/ml). In contrast, the normotensive levels, and to characteristics of the normotensive con-
trols. Several of these factors are considered below.

Number of Subjects

It would be inappropriate to weight studies with
different numbers of patients equally, if small studies,
perhaps involving selected series of patients and there-
fore smaller standard deviations of results, tended to
be positive while larger studies, involving more
generalized patient populations and larger standard
deviations, tended to be negative. In fact, however,
seven of 15 (47%) studies with less than 50 subjects
were positive, and six of 17 (35%) with more than 50
subjects were positive, a nonsignificant difference in
proportions. Average standard deviations of
norepinephrine values were also similar in the two
types of studies (134 vs 138 pg/ml respectively). The
size of the study was therefore unrelated to the fre-
cuency of positive results.

Type of Assay

Of seven studies using a fluorimetric assay, all seven
were positive, while only six of 24 (25%) using a
radioenzymatic assay were positive (x^2 = 3.42, p <
0.001), despite roughly comparable hypertensive-
normotensive mean differences (68 and 49 pg/ml
respectively). The average standard deviation of
norepinephrine levels was significantly greater with
the radioenzymatic technique, for both hypertensive
(160 vs 97 pg/ml, t = 2.46, p < 0.05) and normoten-
sive (144 vs 46 pg/ml, t = 3.12, p < 0.001) groups.
The definition of a “normal” norepinephrine level
depended on the type of assay. For the fluorometric
type, the mean normotensive level was 147 pg/ml,
compared with 251 pg/ml for the radioenzymatic (t =
4.10, p < 0.001). Of the 22 studies using a radioen-
zymatic technique and specifying the enzyme, nine
used phenylethanolamine-N-methyl-transferase
(PNMT) and 13 used catechol-O-methyl-transferase
(COMT). For the PNMT type of radioenzymatic
assay, the mean normotensive level was 283 pg/ml,
compared with 222 pg/ml for the COMT type (t =
2.32, p < 0.05).

Patient Age

Lake, et al.22 have suggested that systematic
differences in group mean age introduced artificial
effects in prior positive studies, because plasma
norepinephrine varied with age and because hyperten-
sives were older than normotensives. Across the 27
studies that listed mean group ages between 20 and 50
years, mean group norepinephrine levels did correlate
significantly with mean group age for the normoten-
sives (r = 0.42, p < 0.05) but not the hypertensives (r
= 0.28). The hypertensives were also older than the
normotensives, by an average of 3.4 years (r = 3.74, p
< 0.001).

Nevertheless, this artificial effect of age would
require that positive studies include older hyperten-
sives 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 norepinephrine levels, 0.15, was negli-
gible.

In contrast, hypertensive-normotensive differences
correlated negatively with mean patient age (r =
-0.37, p < 0.05). Seven of 11 (64%) studies with a
mean patient age less than 40 years were positive,
while three of 17 (18%) with a mean patient age
greater than or equal to 40 years were positive (x^2 =
4.26, p < 0.05).

Severity of Hypertension

If norepinephrine levels varied with the severity of
hypertension, then positive results could have derived
from the inclusion of hypertensives with excessively
high blood pressures. Across the 44 groups in which
mean pressures were reported or calculable, a signifi-
cant correlation of 0.36 (p < 0.05) was obtained
between mean pressures and mean norepinephrine
levels. However, the mean pressures of the hyperten-
sives in the negative studies were actually higher than
those in the positive studies (116 vs 109 mm Hg),
though not significantly so.

Constitution of Control Groups

The available literature provides little information
about whether the controls were inpatients or out-
patients, laboratory workers or newcomers to a
hospital setting, whether they had previously un-
degone phlebotomy, smoked, drank alcohol or coffee
recently, whether they were paid, or how they were
recruited.

The sources of control subjects varied from patients
with “various neurological disorders”19 to patients
recovering from uterine hemorrhage, respiratory in-
fecion, or malnutrition,12 to laboratory workers,13 to
patients detected on population screening,17 to clinic
frequenters with minor complaints.25 One study
reported lower norepinephrine levels in normotensive
laboratory staff than in other normotensive controls.26
Another found higher levels in normotensive out-
patients than inpatients.26

The majority of studies did not specify blood pressure — or any other — criteria for inclusion in the
normotensive group. Across the restricted interstudy
range of mean normotensive pressure, plasma
norepinephrine correlated 0.34 with mean normoten-
sive pressure — a suggestive but not statistically
significant relationship.
Drug Treatment Status

Twenty-seven of the 32 studies described the drug treatment status of the hypertensives. Five studies included only patients who had not previously been treated with an antihypertensive medication. In the remaining 22 studies, medication had been discontinued 1 to 6 weeks prior to phlebotomy. Across these 22 studies, there was no relationship between mean hypertensive norepinephrine levels and amount of time off medication. The mean norepinephrine level of the previously untreated hypertensives (288 pg/ml) was similar to that of the previously treated hypertensives (263 pg/ml).

Sample Handling and Collection

Among the 24 studies reporting their phlebotomy technique, the proportion of positive studies using venepuncture was not significantly different from that using an indwelling catheter. To the extent data were available, the time of day when sampling was done and the length of time the patients were supine prior to sampling were unrelated to the frequency of significant hypertensive-normotensive differences.

Only five studies included information about the kinds of collection tubes used, additives, and length and temperature of storage prior to performing the assay. Yet these mundane points may crucially influence the outcome of a study. For instance, since catecholamine levels may decrease with time in storage,6 obtained hypertensive-normotensive differences may be artfactually decreased when the investigator samples a preponderance of elderly normotensives near the end of the study in order to achieve age matching with the usually older hypertensives.

Discussion

The vast majority of studies of norepinephrine in patients with essential hypertension and in normotensive controls have reported higher mean levels in the hypertensives. To the extent plasma norepinephrine reflects sympathetic activity, this finding supports the hypothesis that sympathetic activity is increased in essential hypertension. Only about two-fifths of the studies, however, reported statistically significant hypertensive-normotensive differences, leading to the effort, in the present study, to identify factors differentiating positive from negative studies.

Hypertensive norepinephrine levels in the positive studies did not differ from those in the negative studies. This argues against the influence of a variably represented hyperadrenergic subgroup. In contrast, normotensive levels were lower and less variable in the positive studies. Unfortunately, the published literature has virtually ignored the sources, characteristics, and treatment of the normotensive controls.

The likelihood of positive results depended on the type of assay used to measure plasma norepinephrine. The radioenzymatic assay was associated both with a lower frequency of positive results and greater interstudy standard deviations than the fluorimetric. "Normal" norepinephrine levels varied by up to 100% across assay types. The available literature provides no clues about why the results should have been so assay-dependent.

The age factor has obscured the role of plasma norepinephrine, since norepinephrine tends to increase with age and since hypertensives have been older than normotensives. Hypertensive-normotensive differences in norepinephrine did not derive from the artificual effects of poor age matching. On the other hand, the largest hypertensive-normotensive differences occurred when the patients — and controls — were relatively young. Further, the age-norepinephrine relationship was statistically significant across the normotensive but not the hypertensive groups. These two findings are consistent with the hypothesis that elevated resting plasma norepinephrine levels characterize a proportion of young patients with essential hypertension.

The available literature has paid inadequate attention to the interactions among several potential intervening variables that may mediate the relationship between plasma norepinephrine and blood pressure. These include thyroid function, the renin-angiotensin-aldosterone axis, plasma volume, sodium balance, alpha- and beta-receptor sensitivity, and the psychological stress associated with hospitalization, diagnostic maneuvers, and the patient’s awareness of the disease. A comprehensive understanding of norepinephrine in essential hypertension will require measurement of or control for these factors.

In summary, three factors differentiated positive from negative studies: 1) normotensive control values; 2) type of assay; and 3) age of the patient population. How and why these factors exert their effects are matters for future research.

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