Relationship Between Plasma Norepinephrine and Sympathetic Neural Activity

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SUMMARY For circulating norepinephrine (NE) to reflect sympathetic activity validly, plasma NE should show an intensity-dependent increase during sympathetic stimulation and decrease during sympathetic inhibition, and circulating NE should correlate with more directly obtained measures of sympathetic activity. Review of published evidence indicates that NE in peripheral plasma satisfies these criteria. However, models used to explain the relationship between circulating NE and sympathetic activity must take into account processes intervening between the synaptic cleft and free NE in the circulation and, since sympathetic outflow is regionalized, the contributions of specific vascular beds to circulating NE. In this report a model is presented where removal processes for NE are viewed as acting in series to produce a gradient in NE concentrations from synapse to plasma, and where the relative contributions of specific vascular beds are calculated from the arteriovenous difference in plasma NE across those beds and the percentage of cardiac output distributed to them. In general, venous plasma NE provides a useful estimation of average sympathetic outflow.

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KEY WORDS • norepinephrine • epinephrine • catecholamines • sympathetic nervous system • hypertension • spontaneously hypertensive rat

MANY recent studies have used venous plasma norepinephrine (NE) concentrations as an index of sympathetic neural activity in humans, and several of these studies have reported plasma NE to be increased in some patients — in particular, young patients — with essential hypertension.1-2 In general, these studies have not critically evaluated the relationship between sympathetic outflow and circulating NE. An understanding of the factors determining that relationship is crucial for interpreting NE levels in terms of sympathetic neural activity in disease states such as essential hypertension. In this report we discuss the validity of antebrachial venous plasma NE for clinical evaluation of sympathetic function, taking into account the factors known to intervene between sympathetically mediated NE release and levels of NE in venous plasma.

For circulating NE to be a valid reflection of sympathetic activity, several criteria must be met: 1) during stimulation of sympathetic outflow, plasma NE should increase in proportion to the intensity of stimulation; 2) during inhibition of sympathetic outflow, plasma NE should decrease, with the extent of decrease similarly related to the extent of inhibition; and 3) plasma NE levels should correlate with more directly obtained measures of sympathetic activity in resting individuals.

Any model relating circulating NE to sympathetic activity must take into account the several processes determining the extent of "spillover" from the synaptic cleft into the general circulation, and, since sympathetic outflow is regionalized and variable, take into account the contributions of specific vascular beds to circulating NE. In this report we describe such a model.

Background Review

Sources of Circulating Norepinephrine

Norepinephrine in the body occurs in tissue of neural crest origin — sympathetic nerve endings, the adrenal medulla, and other chromaffin tissue — and in the brain. Since little if any NE secreted in the brain appears unchanged in the bloodstream, and since extra-adrenomedullary chromaffin tissue atrophies soon after birth, the predominant sources of circulating NE in humans are sympathetic nerve endings and the adrenal medulla.

Although the adrenal medulla secretes NE, the adrenomedullary contribution to circulating NE is usually very small. Adrenalectomy in humans dramatical-
ly decreases circulating epinephrine (E) levels and urinary E excretion, but circulating NE levels and its urinary excretion are unaffected. On the basis of comparing adrenal venous with peripheral venous E and NE concentrations, Planz estimated that 7.5% of circulating NE in peripheral blood derives from the adrenal gland, while Brown et al. estimated that 2% or less has an adrenal source.

During stress, it is possible that the relative contribution of adrenomedullary secretion to circulating NE is enhanced. Adrenal-demedullated rats show attenuated circulating NE responses to stress. Although epinephrine can act presynaptically to enhance NE release from sympathetic nerve endings, it is unlikely that the absence of E after adrenalectomy attenuates the plasma NE response, because bretylium, which inhibits sympathetic neural NE release, does not abolish the plasma NE response to stress except in adrenalectomized rats. Estimates of the adrenomedullary contribution to circulating NE in stressed animals range from 30%-45%. In humans, the ratio of NE to E in adrenal blood does not change with surgical stress. Increased adrenomedullary secretion of both catecholamines during stress, however, would be expected to increase the adrenomedullary contribution to circulating NE.

Although the evidence is indirect, circulating NE probably derives largely from the sympathetic innervation to vascular walls — especially to small arteries and arterioles which also provide the main source for peripheral resistance and therefore crucially influence blood pressure. The extent of "spillover" of NE into the bloodstream followed by sustained release at a lower rate, whereas NE released at a constant rate from sympathetic nerve endings diffuses along several pathways before reaching the general circulation, so that the effect of endogenous NE release on circulating NE resembles a continuous infusion.

In humans, plasma catecholamine responses have been assessed during a variety of stimuli thought to activate the sympathetic nervous system. Orthostasis, isometric and isotonnic exercise, psychological stress, hypoglycemia, cold, pain, vasodilators, caffeine, cigarette smoking, and the Valsalva maneuver all evoke increases in plasma catecholamine levels. During sustained sympathetic stimulation of pithed rats, about 5 minutes are required before plasma NE stabilizes, but plasma epinephrine levels plateau within about 15 seconds. Removal mechanisms for NE and E do not differ sufficiently to account for this finding. Perhaps the adrenal medulla responds to sympathetic stimulation by a sudden, massive "bolus" into the bloodstream followed by sustained release at a lower rate, whereas NE released at a constant rate from sympathetic nerve endings diffuses along several pathways before reaching the general circulation, so that the effect of endogenous NE release on circulating NE resembles a continuous infusion.

In laboratory animals, the ganglionic blocker, chlorisondamine, reliably decreases circulating NE, as does guanethidine, which inhibits NE release from sympathetic nerve endings. Physical disruption of sympathetic outflow by pithing or by cervical spinal cord transection also decreases circulating NE. Disruption of the sympathetic neural supply to the kidney and to the spleen decreases the efflux of NE from these beds. On the other hand, NE responds dramatically to exercise and to orthostasis, and sympathomimetic amines do not consistently increase circulating E. The sympatholytic agent, 6-hydroxydopamine, exerts a somewhat complex effect on circulating NE, because, while it destroys sympathetic nerve endings, there is a marked compensatory adrenomedullary secretion as indicated by plasma E. No report has been made of sympatholytic agents increasing circulating NE levels in animal models. In pithed rats, the entire sympathetic outflow can be cord transected also decreases circulating NE. Sympathetic Stimulation and Circulating Norepinephrine

In pithed rats, the entire sympathetic outflow can be stimulated electrically using as an electrode the metal rod used to pith the animal. Pithing eliminates reflexive circulatory controls. In a pithed rat preparation, the increment in arterial plasma NE varies directly with the intensity or frequency of sympathetic stimulation. Similarily, stimulation of the sympathetic nerves to the heart, spleen, and kidney results in increased NE release into the venous effluent from those organs. Pressor responses during sympathetic stimulation cannot be attributed to the associated increments in circulating NE, because NE infused to similar increments produces no pressor response. Rather, increments in circulating NE during sympathetic stimulation reflect the much higher concentrations of NE at the neuroeffector junctions. In humans, circulating NE does not produce important metabolic or circulatory effects until levels exceed about 1800 pg/ml, although detectable increases in blood pressure can occur at considerably lower concentrations, especially in patients with autonomic dysfunction.

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described the effects of 6-hydroxydopamine administration in adrenal-demedullated animals; this combination is generally lethal.

Patients who have undergone sympathectomy for Raymond's phenomenon have low plasma NE in the venous effluent of the sympathectomized arm. Plasma NE levels also are low in paraplegics, patients with diabetic autonomic neuropathy, and in idiopathic orthostatic hypertension apparently due to peripheral sympathetic failure. Clonidine, which appears to act centrally to inhibit sympathetic outflow, decreases circulating NE in humans, as does debrisoquine, which interferes with the transmission of sympathetic impulses by postganglionic blockade, and the ganglionic blocker, pentolinium.

Measurement of circulating plasma NE levels in patients with different orthostatic hypertensive syndromes has increased our understanding of autonomic dysfunction and indicated limitations of measuring only resting, supine plasma NE levels.

The syndrome of progressive autonomic failure (PAF) can occur alone (idiopathic orthostatic hypotension, IOH) or can be associated with a central neural disorder (multiple system atrophy, MSA). In patients with MSA, supine, resting NE levels are normal, but patients with IOH show low levels. In neither group of patients does plasma NE increase upon standing, although a measurable but subnormal increase can occur in patients with mild dysfunction. The normal basal NE level in MSA indicates that the peripheral sympathetic nervous system is relatively intact but not activated appropriately in response to a postural stimulus. In contrast, the low supine NE levels in patients with IOH suggest that they suffer actual degeneration or complete lack of stimulation of peripheral noradrenergic neurons. As indicated below, it is possible that even patients with peripheral autonomic dysfunction may show nearly normal plasma NE if NE removal processes are slowed.

Patients with IOH or MSA differ from control subjects and from each other in their pressor responses to infused norepinephrine. In IOH and MSA, there is an increased slope of the curve relating blood pressure to plasma NE, reflecting abnormal baroreceptor modulation of pressor responses. This abnormality also is seen in response to angiotensin II, a non-adrenergic pressor. It appears that postsynaptic receptors within the cleft are activated appropriately in response to a postural stimulus. In contrast, the low supine NE levels in patients with IOH suggest that they suffer actual degeneration or complete lack of stimulation of peripheral noradrenergic neurons. As indicated below, it is possible that even patients with peripheral autonomic dysfunction may show nearly normal plasma NE if NE removal processes are slowed.

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MSA and IOH therefore appear to be disease entities with different loci for abnormalities in sympathetic nervous system function. Measuring only resting, supine NE levels in patients with orthostatic hypertensive syndromes may overlook an abnormality in sympathetic responsiveness.

**Resting, Sympathetic Tone and Basal Circulating NE**

In animals, insertion of indwelling vascular catheters for blood sampling is required to ensure that circulating NE levels are not elevated by handling or other stressors. The relationship between directly recorded sympathetic neural activity and plasma NE in individual, alert, resting animals has not been reported.

Wallin et al. recently measured sympathetic activity in humans by quantifying the frequency of pulse-synchronous bursts in the peroneal nerve. Resting sympathetic activity stayed surprisingly constant with time in individual subjects but varied among subjects. Antecubital venous plasma NE obtained on widely separate occasions was directly related to the measured sympathetic activity. Directly measured sympathetic neural activity, as well as plasma NE, increased with age and approximately doubled with standing.

In summary, abundant evidence supports the hypothesis that circulating NE levels are related to sympathetic neural activity in humans and animals. Exactly how they are related requires careful consideration of the factors for NE removal that operate between the synapse and the general circulation, and the relative contribution of various vascular beds to circulating NE. Our concept, described below, for the relationship between sympathetic neural activity and circulating plasma NE takes these into account.

**Model for Estimating Sympathetic Neural Activity in Disease States**

**Norepinephrine Removal Processes**

Figure 1 is a diagram of the processes intervening between the synaptic cleft and the circulation. Most endogenously released NE is removed by Uptake, an energy-requiring, nonstereoselective process that transports NE back into the prejunctional axon. Some released NE acts on postsynaptic alpha-adrenoceptors. It appears that postsynaptic receptors within the cleft are mainly alpha-1 adrenoceptors, whereas alpha-2 receptors are located extrasynaptically. Blockade of alpha-1 receptors attenuates the pressor response to sympathetic stimulation more than to injected NE, whereas alpha-2 blockade attenuates the pressor response to injected NE more than to sympathetic stimulation. Presynaptic alpha-2 receptors modulate release of NE. Released NE also acts at beta-1 receptors, but the concentration of those receptors on vascular muscle is probably low. NE that escapes Uptake, may be removed by Uptake, another active, nonstereoselective process that transports NE into non-neural cells, such as smooth cells. NE also can be removed by nonspecific diffusional and binding processes. In non-neural cells, NE is metabolized mainly by O-methylation, whereas in neurons it is metabolized mainly by monoamine oxidase.
Manipulation of these removal processes will alter the relationship between sympathetically mediated NE release and NE in the general circulation. For instance, Uptake, blockade with desipramine decreases the gradient in NE concentration between the synapse and plasma (Z. Zukowska-Grojec, M.A. Bayorh, I.J. Kopin, and D.S. Goldstein, unpublished observations), so that during NE infusion, the pressor response is enhanced and during sympathetic stimulation, the circulating NE response is enhanced.

The gradient in NE concentration between synapse and plasma can be viewed as the product of a series of the several removal processes (Uptake, Uptake, diffusion, and nonspecific binding) (fig. 2). Since the predominating uptake processes are first-order reactions, during a steady state sustained by sympathetic stimulation or NE infusion, the proportion of NE remaining after passing each uptake site is constant. The fraction, , remaining after passing all the NE removal sites is the product of the fractions, , , ..., where is the fraction remaining after removal process n. Similar reasoning can apply to any number of such sequential removal sites producing a concentration gradient. To the extent Uptake, participates in the removal of NE, Uptake, blockade will increase , to , a value closer to unity, and thereby decrease the concentration gradient between synapse and plasma. A prediction of this model, which we have tested and confirmed (authors’ unpublished observations), is that Uptake, blockade will increase the circulating NE levels associated with sympathetic stimulation to a given pressor response and will augment the pressor response for a given increment in plasma NE during exogenous NE infusion.

Several reports have described the kinetics of disappearance of injected, tracer-labelled NE from the plas-
ma of patients with essential hypertension. In
general, no overall, statistically significant prolonga-
tion of NE disappearance has been reported, casting
doubt on the importance of abnormal removal pro-
cesses in producing the elevated circulating NE levels
seen in some patients with essential hypertension.
Esler et al. have noted that in some patients with
essentials hypertension, the first half-life of the plasma
disappearance of injected NE, which they attributed to
Uptake, was prolonged. We also have observed that,
when the isoproterenol:NE ratio is used as an index of
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infusion of tracer-

**Regional Sympathetic Outflow**

Sympathetic outflow to the various vascular beds is
different. Thus, hypothalamic stimulation and
baroreceptor stimulation result in patterns of sympa-
thetic responses that are similar qualitatively in differ-
ent nerves but not quantitatively. Regional differences
in sympathetic outflow account for differences in pat-
terns of NE and E responses to several stresses.

Table 1 shows summary results derived from studies
of humans, describing the arteriovenous differences
for NE as a function of the organ bed. The decreases in
plasma NE from artery to vein in most beds are small
(about 25% of arterial). In view of the errors inherent
in the assay techniques used to measure NE, these data
are of somewhat limited reliability. A few conclu-
sions, however, seem justified: first, in most beds, venous NE levels exceed arterial; second, the liver
extracts a large proportion of NE, resulting in low hepatic venous concentrations; third, the lungs
extract up to 25% of the NE in their arterial blood
supply.

By weighting the obtained venoarterial (V-A) dif-
ference in NE for the percentage of cardiac output
reaching a given bed, the relative contribution of the
bed to mixed venous NE can be calculated (fig. 3). Thus,
although a spectacular net increment in NE oc-
curs across the adrenal glands, the importance of their
contribution to circulating NE is small because only a
small percentage of the cardiac output is distributed to
the adrenals. The net extraction of NE by the lungs is
important because they receive the entire cardiac out-
put. This weighing explains why cardiac pacing in
humans increases the V-A difference in NE across the
heart but does not significantly increase peripheral ar-
terial NE levels and why decreased NE removal in the
lungs of patients with pulmonary hypertension can be
associated with increased plasma NE without in-
creased sympathic activity.

Since E derives solely from the adrenal medulla,
investigators have used the V-A difference for E as an
index of NE extraction in given vascular beds. The
assumption is that E and NE are removed similarly in
tissues. The validity of this assumption has never been

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**Table 1.** Arteriovenous Differences in Plasma Norepinephrine
in Several Vascular Beds in Humans

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Values estimated from figures when necessary. Patients suffered various disorders, but in a given study involving both patients and
controls, only control values were considered.

N = number of subjects; NEa = arterial norepinephrine, pg/ml; NEv = venous norepinephrine, pg/ml; V-A = venoarterial difference,
pg/ml; weighted means = weighted for number of subjects in each study.
directly tested in humans, but evidence from patients with pheochromocytoma is suggestive, because those patients, with elevated plasma NE and E due to release by the tumor, show similar percent decreases in NE and E across several beds. If the V-A difference for E does provide a measure of NE extraction, then the amount of sympathetically mediated NE release can be estimated by adjusting the obtained V-A difference in NE for the amount of NE extracted in that bed. When this approach was applied to the data reported by Kjeldsen et al., patients with essential hypertension showed dramatically greater sympathetically mediated NE release in the arm than did age-matched normotensive controls.

The kinetics of disappearance of tracer-labelled injected NE and E from plasma may not be identical, however. In humans, clearance of E from plasma appears to exceed somewhat that of NE. In mice, tissue uptake is more prominent for NE than E. Whether these results are of practical importance in interpreting V-A differences in NE and E is unknown.

Since the V-A difference in NE across the arm in resting healthy individuals is small, levels of NE in antecubital venous blood appear to provide a reasonable estimate of levels in arterial plasma. Extreme stress may disrupt this relationship. In patients with essential hypertension, the V-A difference across the arm could be substantial, in which case venous plasma NE levels could overestimate sympathetic tone.

The patterns of NE and E responses to different environmental stresses are consistent with regional regulation of sympathetic outflow. Psychological stress and hypoglycemia produce a predominantly adreno-medullary response. Since E derives only from the adrenal medulla, circulating levels of E will respond dramatically to sympathoadrenal stimulation. NE released from the adrenal medulla represents only a small fraction of mixed venous or arterial NE, so that sympathoadrenal activation produces only small increments in circulating NE. In contrast, during orthostasis or moderate exercise, the relative contribution from skeletal muscular beds is enhanced; splanchnic blood flow and therefore hepatic removal are decreased, resulting in large increments in circulating NE. During stimulation of central sympathetic outflow, extremes of exercise, anoxia, shock, or severe hypoglycemia, combined adrenomedullary discharge and NE release from sympathetic nerve endings result in increased circulating levels of both catecholamines.

Studies of plasma NE and E in patients with essential hypertension and in normotensive controls have indicated that hypertensives with elevated NE do not necessarily have elevated plasma levels of E, and vice versa. When "total catecholamines" have been reported, virtually all studies have found significantly higher levels in the hypertensives. It is possible, therefore, that among the hypertensive population, some patients have accentuated sympathetic outflow to extra-adrenal beds and other accentuated sympathetic outflow to the adrenals. An isolated increase in splanchnic sympathetic activity, for instance, could increase circulating E due to adrenomedullary secretion without altering plasma NE levels significantly because of hepatic extraction of the NE in the portal venous drainage of the splanchnic bed. On the other hand, an increase in renal sympathetic nerve activity could increase circulating NE because of the enhanced V-A difference in NE across the kidney and the significant percent of cardiac output distributed to it. When the sum of NE + E is considered, the hypertensives as a whole may be better differentiated from the normotensives than when levels of either catecholamine alone are considered.

In spontaneously hypertensive rats, it is unclear whether resting levels of NE are elevated. Older methods of blood sampling, especially decapitation, are now known to be profound stimuli for NE and E release, and since spontaneously hypertensive rats show excessive catecholamine responses to stress, older positive studies may not have applied to the issue about resting sympathetic tone. A recent study in this area found that the difference in SHR and WKY NE levels was age-dependent; that is, the SHR-WKY difference was significant only for young rats. This finding seems very similar to an observation we have reported, virtually all studies have found significantly higher levels in the hypertensives. It is possible, therefore, that among the hypertensive population, some patients have accentuated sympathetic outflow to extra-adrenal beds and other accentuated sympathetic outflow to the adrenals. An isolated increase in splanchnic sympathetic activity, for instance, could increase circulating E due to adrenomedullary secretion without altering plasma NE levels significantly because of hepatic extraction of the NE in the portal venous drainage of the splanchnic bed. On the other hand, an increase in renal sympathetic nerve activity could increase circulating NE because of the enhanced V-A difference in NE across the kidney and the significant percent of cardiac output distributed to it. When the sum of NE + E is considered, the hypertensives as a whole may be better differentiated from the normotensives than when levels of either catecholamine alone are considered.
Conclusions

The available evidence indicates that venous plasma NE provides a reasonable if indirect index of sympathetic neural activity, and once abnormalities in removal processes or in specific vascular beds are excluded, can be used to evaluate average sympathetic tone in disease states in humans. The relationship between NE released into the synaptic cleft and NE in the venous effluent from a given vascular bed can be expressed in terms of a concentration gradient, produced especially by Uptake. One can estimate the contribution of a vascular bed to circulating NE by multiplying the venoarterial difference in NE across the bed by the percent of cardiac output distributed to it. Mixed venous NE reflects the averaged contributions from the various beds and therefore estimates overall sympathetic tone.

References

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