Norepinephrine Removal and Release in the Forearm of Healthy Subjects

PETER C. CHANG, JACQUES A. VAN DER KROGT, PIETER VERMEIJ, AND PETER VAN BRUMMELEN

SUMMARY The relevance of local removal and release of norepinephrine (NE) for antecubital venous plasma NE concentration was studied in 22 healthy subjects. Arterial and venous plasma NE and forearm blood flow were measured during 1) intra-arterial infusion of two doses of NE, 2) intra-arterial NE infusion with two doses of sodium nitroprusside, 3) intravenous infusion of NE with intra-arterial infusion of four doses of sodium nitroprusside, and 4) lower body negative pressure of −20 mm Hg for 15 minutes. The venous plasma NE concentration-time curves during the infusions of the two doses of NE indicated first-order kinetics for forearm extraction: forearm NE extraction rate during the low dose infusion was 67 ± 4.1% (SEM) and correlated with basal forearm blood flow ($r = -0.64, p<0.03, n=12$). Local sodium nitroprusside-induced vasodilatation during the intra-arterial and intravenous NE infusions was accompanied by dose-dependent decreases in forearm extraction rates for NE and epinephrine. During lower body negative pressure, taking into account the high basal forearm extraction rate for NE, local and systemic release of NE was indicated by increases in arterial and venous plasma and the venous-arterial plasma NE concentration difference ($p<0.05$ for all). These data show that removal of NE from forearm circulation is a process with a high extraction ratio obeying first-order kinetics and that this extraction process inversely relates to forearm blood flow. Thus, antecubital venous plasma NE is likely to be derived mainly from local release and not from the arterial plasma NE input. (Hypertension 8: 801–809, 1986)

KEY WORDS plasma norepinephrine • plasma epinephrine • norepinephrine release • norepinephrine extraction • epinephrine extraction • forearm blood flow • sodium nitroprusside • lower body negative pressure

The plasma norepinephrine (PNE) concentration in blood taken from a forearm vein is a widely used estimate of overall sympathetic nervous system activity. Although several studies have shown a correlation between venous PNE and the activity of the sympathetic nervous system,1-3 this approach has also been criticized.4,5 For instance, Mancia et al.6 showed that alterations in sympathetic tone and blood pressure induced by manipulating the baroreflex were not reflected by alterations in plasma catecholamine concentrations. Also, during experimental mental stress, changes in sympathetic nerve activity are not paralleled by changes in venous PNE.7,8

Apart from local neuronal release,7,9,10 the removal of norepinephrine (NE)11-13 appears to be an important determinant of venous PNE. Various rates of NE release and removal that have been reported in the human forearm were suggested to be related to local sympathetic nerve activity and, possibly, to forearm blood flow (FBF) level.11,12

The aim of the present study was to evaluate the local removal and neuronal release of NE in healthy subjects as determinants of antecubital venous PNE and to study the importance of FBF in this respect.

Materials and Methods

Subjects

The study included 22 healthy male volunteers. Some relevant clinical characteristics are given in Table 1. Their medical history and results of physical examination and routine laboratory tests showed no
evidence of cardiovascular or other disease. All medication was stopped 2 weeks before the study began. Informed consent was obtained from all subjects, and the study protocol was approved by the Medical Ethics Committee of the Leiden University Hospital.

Procedures
All experiments started at 0900 and were performed in a quiet room with a constant temperature of 20°C with the subjects in the supine position. On the day of the study, all subjects had a light breakfast and refrained from drinking caffeine-containing beverages and from smoking. After local anesthesia of the skin, the brachial artery of the nondominant side was cannulated retrogradely with a 5-cm long, 1.3-mm thick cannula for intra-arterial (i.a.) infusion of drugs, blood sampling, and blood pressure monitoring with a Statham P23Id pressure transducer (Gould, Oxnard, CA, USA). In the same arm, a deep cubital vein also was cannulated for i.a. infusion of NE, 1.18 pmol/kg/min i.a., was infused in six subjects for 8 minutes. Venous blood was sampled at 0, 2, 4, and 8 minutes, and arterial samples were drawn at 0 and 8 minutes. A second NE infusion of 1.18 pmol/kg/min then was given for 16 minutes with a concomitant i.a. infusion of sodium nitroprusside (NIP): 13.42 pmol/kg/min from — 5 to 8 minutes and 40.27 pmol/kg/min from 8 to 16 minutes of this NE infusion. At least 20 minutes of rest was allowed between all infusions. Venous blood samples were drawn at 0, 2, 4, 8, 10, 12, and 16 minutes, and arterial blood was sampled at 0 and 16 minutes. Measurements of FBF were made immediately before and during the last 2 minutes of each dose.

In the third experiment, four subjects received an i.v. infusion of NE, 7.1 nmol/min, for 35 minutes. Blood flow in the contralateral hand was excluded by a wrist cuff from the 10th to the 35th minute, and NIP, 7, 13, 37, and 91 pmol/kg/min i.a., respectively, in each subject, was infused from the 15th to the 35th minute. At — 2, 0, 2, 4, 10, 15, 20, 25, 30, and 35 minutes, paired arterial and venous blood samples were taken, and FBF was measured at 15, 20, 25, 30, and 35 minutes of this infusion.

In the fourth experiment, the change in local neuronal release of NE was investigated in six other subjects using LBNP as a stimulus for sympathetic nerve activity. An LBNP of — 20 mm Hg, as registered by a pressure transducer, was reached within 5 seconds and was applied continuously for 15 minutes. Venous and arterial blood samples were drawn at 0, 2, 4, 8, and 15 minutes for determination of PNE and PE. Measurements of FBF were made at 15-second intervals.

Drug Solutions, Sample Collection, and Assay
Both l-NE and NIP were prepared according to the "Formularium Nederlandse Apothekers," and were diluted in 0.9% saline and 5% glucose, respectively, for intra-arterial use. The solutions were freshly prepared on the morning of each investigation. Blood samples of 3 ml were collected into heparinized tubes containing 20 μl of 0.2 M reduced glutathione per milliliter of blood and placed on ice. Samples were centrifuged at 4°C and at 3500 g for 15 minutes, and plasma was stored at —70°C until assayed. In each sample, PNE and PE were measured in duplicate by a single isotope radioenzymatic assay.17 All samples from a single subject were run in the same assay. Intra-assay coefficients of variation for PNE and PE were less than 10% in the 0.5 nmol/L range.

Analysis
The half-life of venous PNE was derived from the individual venous concentration–time curves by nonlinear, least-squares curve fitting, using the one-compartmental model: C = A/T(1 − e−αt) + C0, where C,
and $C_0$ are venous PNE at time 0 and $t$ of the infusion, $T$ is the time of infusion, and $A$ and $\lambda$ are parameters to be estimated by curve fitting (procedure NLIN of Statistical Analysis Systems computer package, SAS Institute, Cary, NC, USA). The half-life is equal to 0.693/$\lambda$. The forearm extraction (FE) of circulating NE was calculated using the following equation:

$$FE = A + (V/FPF) - V/A + (V/FPF),$$

where $A$ is arterial PNE, $I$ is i.a. NE infusion rate, PPF (forearm plasma flow) is equal to FBF x forearm volume (in deciliters) x (1 - hematocrit), and $V$ is venous PNE. The FE of $E$ and, in the third experiment, of NE, were calculated from the equation $FE = A - V/A$, where $A$ and $V$ are arterial and venous PE and PNE, respectively. Total forearm clearance of NE was estimated by multiplying FE by FBF. Forearm volume was measured by noting the volume of water displaced by forearm and hand and then subtracting the volume of water displaced by the hand.

The systolic and diastolic blood pressures and heart rate recorded immediately before and at the end of each infusion were used for analysis. The FBFs in the LBNP experiment are mean values of measurements made within 2-minute periods. The FBF values used for analysis in the infusion studies are mean values of at least six consecutive measurements.

Statistical analysis was performed using the SAS computer package with two-way analysis of variance with correction for repeated measures and, where appropriate, with two-tailed Student’s $t$ test for paired observations. Values are presented as means ± SEM.

### Results

The relevant clinical data of the 22 subjects are summarized in Table 1. Heart rate was not influenced significantly by any of the infusions. After 15 minutes of the i.v. infusion of NE, 7.1 nmol/min, systolic and diastolic blood pressure increased from 129.8 ± 6.3 to 139.3 ± 4.7 mm Hg ($p < 0.05$) and from 76.3 ± 3.8 to 71.5 ± 3.9 mm Hg ($p < 0.05$), respectively. No further significant changes in systolic or diastolic blood occurred during this or any other infusion experiment.

Table 2. Arterial and Venous Plasma Levels and Forearm Extraction of Norepinephrine and Epinephrine and Forearm Blood Flow in 12 Healthy Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Experiment 1 ($n = 6$)</th>
<th>Experiment 2 ($n = 6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNE (nmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial, preinfusion</td>
<td>1.31±0.20</td>
<td>1.24±0.16</td>
</tr>
<tr>
<td>Arterial, end of infusion*</td>
<td>11.71±1.19$</td>
<td>$</td>
</tr>
<tr>
<td>Venous, preinfusion</td>
<td>1.24±0.15</td>
<td>1.31±0.13</td>
</tr>
<tr>
<td>Venous, end of infusion</td>
<td>2.51±0.22§</td>
<td>3.81±0.47§</td>
</tr>
<tr>
<td>PE (nmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial, preinfusion</td>
<td>0.41±0.09</td>
<td>0.32±0.05</td>
</tr>
<tr>
<td>Arterial, end of infusion</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Venous, preinfusion</td>
<td>0.16±0.03$</td>
<td>$</td>
</tr>
<tr>
<td>Venous, end of infusion</td>
<td>0.13±0.02</td>
<td>0.13±0.01</td>
</tr>
<tr>
<td>End of infusion forearm extraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>77.4±3.1</td>
<td>84.6±3.0$</td>
</tr>
<tr>
<td>E</td>
<td>64.8±10.6</td>
<td>56.8±4.3</td>
</tr>
<tr>
<td>Forearm blood flow (ml/dl/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion</td>
<td>1.9±0.4</td>
<td>1.6±0.3</td>
</tr>
<tr>
<td>End of infusion</td>
<td>1.6±0.2</td>
<td>1.3±0.2$</td>
</tr>
</tbody>
</table>

Values are means ± SEM. NE = norepinephrine; NIP = sodium nitroprusside; E = epinephrine.

*Calculated.

†$p < 0.001$, ‡$p < 0.01$, §$p < 0.05$, compared with preinfusion values; †$p < 0.05$, ‡$p < 0.01$, compared with arterial values; ‡$p < 0.01$, **$p < 0.05$, compared with values for NE, 1.18 pmol/kg/min.

††After 5 minutes of NIP, 13.42 pmol/kg/min i.a.
Venous plasma norepinephrine concentration (PNE) during infusion of two doses of norepinephrine into a brachial artery in six healthy subjects.

**Figure 1.**

This decrease was only significant during the high dose (p < 0.05; see Table 2). At the end of the high dose infusion, FBF was significantly lower than at the end of the low dose infusion (p < 0.05; see Table 2). The removal of infused NE, expressed as the FE of NE, increased significantly from 77.4 ± 3.1% at the end of the 1.18 pmol/kg/min infusion to 84.6 ± 3.0% at the end of the 2.36 pmol/kg/min infusion (p < 0.01; see Table 2), while the forearm clearance of NE did not change significantly. Thus, the removal process of infused NE, in the dose range used, did not appear to change significantly. This, the removal of infused NE, in the dose range used, did not appear to be saturated, and the FE of NE changed inversely with the changes in FBF. Preinfusion arterial PE was significantly higher than the venous value in both infusions (see Table 2), while the forearm clearance of NE did not change significantly. Thus, the removal process of infused NE, in the dose range used, did not appear to be saturated, and the FE of NE changed inversely with the changes in FBF. Preinfusion arterial PE was significantly higher than the venous value in both infusions (see Table 2), while the forearm clearance of NE did not change significantly.

In the second experiment, the preinfusion values of arterial and venous PNE did not differ significantly (Figure 2; see Table 2). During both i.a. NE infusions steady state levels of venous PNE were reached within 7 minutes (see Figure 2). The half-life of venous PNE was 93 ± 25 seconds for the 1.18 pmol/kg/min infusion of NE and decreased to 68 ± 11 seconds (p < 0.05) during the addition of NIP, 13.42 pmol/kg/min. The NE infusion alone did not significantly change FBF. In the second part of this experiment, the NIP infusion significantly increased FBF (p < 0.01; Figure 3; see Table 2). The addition of NE to this NIP infusion decreased FBF significantly, and FBF again rose on infusion of the higher NIP dose (p < 0.01; see Table 2 and Figure 3). The FE of NE at the end of the infusion of NE, 1.18 pmol/kg/min, alone was 57.1 ± 4.9%. Supplemented with the values of the same NE dose infusion from the first experiment, the FE of NE was 67.1 ± 4.1% and correlated inversely with basal FBF (r = -0.64, p < 0.03, n = 12; Figure 4A). When FBF was increased by i.a. infusion of the two doses of NIP, the FE of NE decreased to 47.4 ± 4.8% and 39.7 ± 4.2%, respectively (p < 0.05 for both; see Table 2 and Figure 3), while the clearance of NE significantly increased (p < 0.01; see Figure 3). Figure 4B shows the relation between individual values of FE of NE and FBF in the first and second experiments. During both infusions, the arterial PE values at the beginning and end of infusion were significantly higher than the venous values (see Table 2). The venous PE values were not significantly influenced by the single NE infusion but showed an increase during infusion of the two NIP doses (p < 0.01; see Table 2), while the FE of E decreased from 59.8 ± 4.3% at the end of the single NE infusion to 33.3 ± 2.9% and 36.6 ± 5.3% (both, p < 0.01; see Table 2) at the end of the low and high dose NIP infusions, respectively.

In the third experiment, the preinfusion arterial and venous PNE values were not significantly different (Figure 5). Steady state levels of venous and arterial PNE were reached after approximately 10 minutes (see Figure 5). From the 10th to the 15th minute the venous PNE decreased 0.29 ± 0.09 nmol/L (p < 0.05) and the FE of circulating NE decreased from 53.4 ± 7.2 to 30.7 ± 2.8% (p < 0.05; see Figure 5), and the FE of E decreased from 52.0 ± 7.8 to 33.9 ± 5.9% (not significant; data not shown). These results indicate that the FE of circulating NE is flow-dependent.

When maximal differences in basal blood pressure and heart rate values were considered, a transient decrease in systolic blood pressure (9.7 ± 3.0 mm Hg; p < 0.05) and increase in heart rate (6.7 ± 4.6 beats/min; not significant) were noted within 30 seconds after LBNP was begun. After this transient fall in systolic blood pressure and rise in heart rate, these parameters did not differ from the basal values. Changes in arterial and venous PNE and PE and in FBF during LBNP of -20 mm Hg for 15 minutes are summarized in Figure 6. The FBF showed a significant decrease after 2 and 4 minutes of LBNP (p < 0.05; see Figure 6). All other FBF values did not differ significantly from basal values. Arterial and venous PNEs reached their maximum at 4 minutes of LBNP (see Figure 6). Arterial PNE increased from 1.18 ± 0.14 to 1.79 ± 0.30 nmol/L (p < 0.05; see Figure 6), and venous
NOREPINEPHRINE HANDLING IN HUMAN FOREARM/Chang et al.

Figure 2. Venous plasma norepinephrine concentration (PNE) during infusion of one dose of norepinephrine, with and without an infusion of two doses of sodium nitroprusside (NIP), into a brachial artery in six healthy subjects.

Figure 3. Forearm blood flow (FBF), calculated forearm extraction (FE), and clearance (CL) of circulating norepinephrine at the end of infusion of norepinephrine, 1.18 pmol/kg/min, without (A) and with infusion of sodium nitroprusside, 13.42 pmol/kg/min (B) and 40.27 pmol/kg/min (C), into a brachial artery in six healthy subjects. Single (p<0.05) and double (p<0.01) asterisks indicate the significance of difference when compared with A.

PNE increased from 1.09 ± 0.10 to 2.00 ± 0.21 nmol/L (p<0.01; see Figure 6). In all subjects, arterial and venous PNE values during LBNP showed a good correlation, with a correlation coefficient of 0.83 ± 0.04. The venous-arterial difference in PNE increased from a basal value of −0.09 ± 0.07 nmol/L up to a maximum of 0.21 ± 0.12 nmol/L (p<0.05) at 4 minutes of LBNP. Thereafter, arterial and venous PNE values and the venous-arterial PNE differences gradually diminished (see Figure 6). The net overflow of NE (FPF × venous-arterial PNE difference) increased nonsignificantly from −0.36 ± 0.22 nmol/min immediately before LBNP to 0.63 ± 0.37 nmol/min at 4 minutes of LBNP. At all other times during LBNP, the net overflow of NE was not significantly different from the basal values. Arterial and venous PEs tended to increase during LBNP, but the differences compared with basal values were not statistically significant (see Figure 6).

Discussion

This study demonstrates that circulating NE is extensively removed from the human forearm. Under basal conditions we found that individual extraction rates for intra-arterially administered NE varied from 30 to 82%. The mean values were comparable to those reported by others.12, 13 In a study in healthy persons, which used heart rate and blood pressure as a measure of overflowing NE, the removal of intra-arterially administered NE from the forearm was estimated to be on the order of 75%.12 Stjärne et al.,13 using a mixture of radiolabeled NE, albumin, and inulin, estimated the total removal of radiolabeled NE from the forearm circulation of healthy subjects at 65 to 70%, while the specific extraction of NE was approximately 50%. As
FIGURE 4. Forearm extraction (FE) rates for circulating norepinephrine (NE) and forearm blood flow (FBF) at the end of the NE infusion of 1.18 pmol/kg/min in 12 subjects (Panel A). All individual values of the two infusion experiments are shown in Panel B. See Results for details.

FIGURE 5. Venous (○) and arterial (●) plasma norepinephrine concentration (PNE), forearm blood flow (FBF), and forearm extraction (FE) rate of circulating norepinephrine during i.v. infusion of norepinephrine and i.a. infusion of sodium nitroprusside (NIP) in four healthy subjects.
tion, when coronary sinus blood flow was increased by cardiac pacing. This discrepancy may be explained by the much lower basal rate of NE extraction (approximately 30%) found in this vascular bed. Carlson et al. found that the extraction rate of circulating NE in cat skeletal muscle also decreased considerably when an increase in muscle blood flow was superimposed on a steady vasoconstrictor sympathetic nerve stimulation. Recently, the flow dependency of the circulating NE extraction rate was also shown in isolated perfused rat lungs.

In our experiment, the local extraction process of NE obeyed first-order kinetics and was not saturated despite the fact that relatively high arterial PNE concentrations were reached (see Table 2). In fact, this result would be expected because of the reported high $K_m$ values for neuronal NE uptake of 270 nmol/L and for extraneuronal NE uptake of 3.4 μmol/L found in pharmacological experiments.

An effect of the NE infusions on local neuronal release of NE by presynaptic adrenergic receptors could have influenced the results. Although this possibility could have been circumvented by the intra-arterial use of tracer doses of radiolabeled NE, it seems unlikely that the amounts of NE used in the present study influenced local NE release. In fact, the calculated arterial PNE concentrations reached in our experiments are 200- to 1000-fold less than the effective intrasynaptic NE concentration estimated in pithed rats, in the isolated vascular bed of cat calf muscles, and in other isolated animal blood vessels. Kopin et al. argued that the routes for diffusion of NE from the region of the synapse to the blood vessel lumina and vice versa are identical and that it seems unlikely that any removal process along these pathways can distinguish between NE released from nerves and NE originating from the circulation. Thus, assuming that local endogenous NE release is not influenced by an intra-arterial NE infusion in an amount that does not affect local blood flow, the estimate of the FE rate for circulating NE could be used as a measure for the extraction rate of circulating as well as locally released NE. This notion is supported by the fact that calculation of the total muscle NE spillover rate, based on the formula and the value for total muscle plasma flow used by Esler et al. and the data of NE extraction rate and

![Figure 6. Arterial (*) and venous (○) plasma nor-epinephrine (PNE) and epinephrine (PE) concentrations and forearm blood flow (FBF) during 15 minutes of lower body negative pressure (LBNP) of -20 mm Hg in six healthy subjects.](image)

$\text{Organ NE spillover (SO)}$ is defined as $\text{SO} = (V-A) \times Q + A(E \times Q)$, and organ NE release ($R$) is derived from the equation $A \times Q + R = Q \times V + R \times E + A(E \times Q)$ (organ NE input = organ NE output). $Q$ = organ plasma flow; $E$ = extraction; other symbols are defined in Methods. Transformation of these equations results in the formula $\text{SO} = (1-E) \times R$; in other words, organ spillover of NE is the fraction of organ $R$ of NE that escapes local extraction.
basal arterial and venous PNE concentrations from our first and second experiments, gives a total muscle NE spillover rate of 98 and 64 ng/min, respectively, which is in the same range as that estimated with the radiotracer infusion methodology.\(^{29}\)

As the FE of E did not parallel that of NE, our data do not support the view that FE of E could be used as an estimate of the removal of NE.\(^{30}\)

The kinetics of endogenously released NE were studied using LBNP of \(-20\) mm Hg to stimulate local and systemic release of NE. The transient responses of heart rate and intra-arterially registered blood pressure that were noted during the first 30 seconds of LBNP may indicate that sympathetic stimulation was not mediated exclusively by "low pressure" stretch receptors,\(^{31-33}\) but initially also by arterial baroreceptors. Systemic release of NE during LBNP was indicated by a rise in arterial PNE concentration. An increase in local release of NE was demonstrated, taking into account the local high extraction rates for circulating NE, by the increases in venous PNE concentration and net NE overflow. Also, the decrease in FBF flow argues for a marked increase in local neuronal NE release. As even an increase in (calculated) arterial PNE concentration to 11.71 nmol/L in our first experiment did not induce a significant change in FBF, the rise in arterial PNE concentration during LBNP to 1.79 nmol/L seems far too insufficient to have caused the decrease in FBF during LBNP. The measurement of local extraction of NE during LBNP would have required either a low dose intra-arterial infusion of NE or an infusion of radiolabeled NE. However, by extrapolating the NE extraction rates at the various blood flow levels in the infusion experiments to the LBNP experiment, it can be inferred that the increase in venous PNE concentration was derived mainly from enhanced local release.

After an initial rise, the venous and arterial PNE concentrations, and their difference, appeared to decline gradually. This may be explained either by an increase in the extraction rate of NE secondary to the decrease in FBF or by a decrease in sympathetic nerve activity as a result of baroreflex resetting, or by both. Grassi et al.\(^{35}\) reported a sustained increase in venous PNE concentration during LBNP. This discrepancy is most likely due to methodological differences between the two studies.

We conclude that the removal of circulating NE in the human forearm is a process with a high extraction ratio and first-order kinetics that is unlikely to be saturated in physiological conditions. The rate of extraction was found to be inversely related to flow. Thus, under basal conditions, when FBF is relatively low, the antecubital venous PNE concentration will be derived mainly from local NE release and not from the arterial NE input. Only in situations in which changes in muscle sympathetic nerve activity parallel changes in general sympathetic nerve activity does the antecubital venous PNE concentration seem to reflect systemic sympathetic nerve activity (e.g., during LBNP).

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Acknowledgments

The authors are grateful to Mrs. Rina van Ingen-van der Merwe, Mrs. Henny C.N. Kappelle-de Vries, Mrs. Anja H. Piket-Groenen- daal, and Mrs. Kiki Jasper for their excellent technical assistance and secretarial help.

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Norepinephrine removal and release in the forearm of healthy subjects.
P C Chang, J A van der Krogt, P Vermeij and P van Brummelen

Hypertension. 1986;8:801-809
doi: 10.1161/01.HYP.8.9.801

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