

## Plasma catecholamine concentrations in essential hyperhidrosis and effects of thoracoscopic D<sub>2</sub>–D<sub>3</sub> sympathicolysis

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**Abstract.** Essential hyperhidrosis (EH) is caused by a poorly understood overactivity of the sympathetic fibres passing through the upper dorsal sympathetic ganglia D<sub>2</sub> and D<sub>3</sub>. These ganglia are also in the pathway of the sympathetic innervation of the heart and lungs. Therefore, although the predominant sympathetic neurotransmitter at the eccrine sweat glands is acetylcholine, the plasma concentration of noradrenaline (NA) (which is the main sympathetic neurotransmitter at the end organs including the heart and the lungs) may be elevated. Furthermore, as there are some indications for generalized sympathetic overactivity in EH, the plasma concentration of adrenaline (A) may also be elevated. Plasma levels of NA and A were therefore determined in 13 EH patients before and after thoracoscopic D<sub>2</sub>–D<sub>3</sub> sympathicolysis (TS). Preoperative NA and A plasma levels were all within the normal limits used in our laboratory. After TS, mean NA plasma levels are significantly decreased, whereas mean A are unchanged. We conclude that sympathetic overactivity in EH is limited to the upper dorsal sympathetic ganglia and that some of the cardiovascular and pulmonary effects that are observed after TS may be associated with the decrease in NA.

**Keywords.** Adrenaline, catecholamines, essential hyperhidrosis, noradrenaline, sympathectomy, thoracoscopy.

### Introduction

Essential hyperhidrosis (EH), a pathological condition of excessive sweating at the palms of the hands, and often also of the armpits and soles of the feet, is characterized by an increased sympathetic activity at the upper dorsal sympathetic ganglia D<sub>2</sub> and D<sub>3</sub> [1,2]. The D<sub>2</sub> and D<sub>3</sub> sympathetic ganglia are also in the pathway of the sympathetic innervation of the central thoracic organs. Hence, increased sympathetic activity is present not only at the eccrine sweat glands of hands

and arms [3] (neurotransmitter, predominantly acetylcholine [4]), but also at the heart [5,6] and lungs [7] [neurotransmitter, noradrenaline (NA)]. Therefore, the major post-ganglionic sympathetic neurotransmitter NA may be elevated in EH, even although the predominant post-ganglionic sudomotor sympathetic neurotransmitter is cholinergic (acetylcholine). The observed beta blocking-like effect of thoracoscopic sympathicolysis (TS) on cardiac autonomic function [5,6] may therefore be mediated through, or characterized by, TS-induced changes in circulating plasma concentrations of NA.

Adrenaline (A) is released from the adrenal medulla after sympathetic stimulation via middle and lower dorsal ganglia [8]. Although sympathetic overactivity in EH is mainly present at the upper dorsal ganglia, there are some indications of generalized sympathetic activity in EH patients [1]. It is therefore conceivable that circulating plasma A might also be elevated in EH, and may account for some of the cardiac and pulmonary effects observed after TS.

To our knowledge, no previous measurements of plasma catecholamines in essential hyperhidrosis have been made. We therefore measured plasma, NA and A in patients with EH before and after TS.

### Materials and methods

#### Patients

Thirteen patients (six men, seven women, mean age 27.2 ± 9.9 years, range 15–49 years) were studied. Every patient had severe EH that was refractory to conservative treatment. The patients were otherwise in a healthy condition and taking no medication. Informed consent was obtained from every patient.

#### Methods

Plasma catecholamine concentrations (NE and E) were determined 1 day before and 1 day after TS. Plasma

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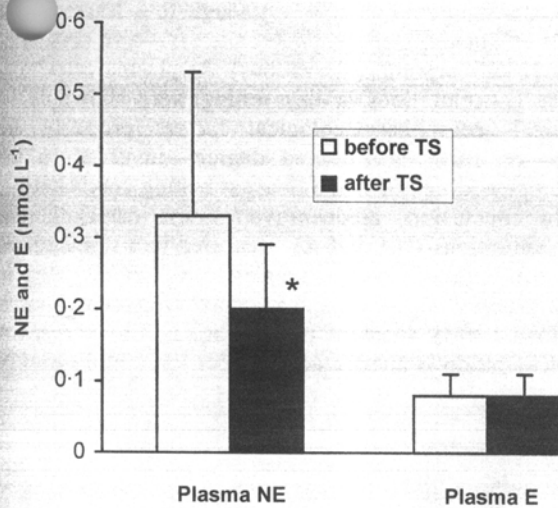


Figure 1. Plasma noradrenaline (NA) and adrenaline (A) levels 1 day before and 1 day after thoracoscopic sympathectomy: mean values (boxes) and SD (whisker) in 13 patients with essential hyperhidrosis.

Statistical analysis

Data are expressed as mean values ± SD. Pre- and post-operative levels were compared using the paired Wilcoxon rank-sum test and P-values <0.05 were considered statistically significant.

Results

Results are shown in Fig. 1. Preoperative plasma NA and A were all within normal limits: mean NA was 0.33 ± 0.2 nmol L<sup>-1</sup> (range 0.14–0.74 nmol L<sup>-1</sup>), and mean A was 0.08 ± 0.03 nmol L<sup>-1</sup> (range 0.05–0.13 nmol L<sup>-1</sup>). None of the NA and 8 of the 13 A measurements were below the detection limit of the assay. In these cases, the detection limit was used for calculations.

TS abolished palmar hyperhidrosis in every patient, thereby confirming the anatomical interruption at the D<sub>2</sub>–D<sub>3</sub> ganglionic level.

After TS, mean A remained unchanged (0.08 ± 0.03 nmol L<sup>-1</sup>), whereas mean NA had significantly decreased to 0.20 ± 0.09 nmol L<sup>-1</sup> (P = 0.035).

Discussion

Our data show that preoperative levels of plasma NA and A carefully obtained at rest are not elevated in EH patients. EH therefore can be considered as a disorder of localized sympathetic overactivity at the D<sub>2</sub>–D<sub>3</sub> upper dorsal ganglionic level, with no (at least in resting conditions) generalized overactivity of the sympathetic nervous system. TS had no effect on plasma levels of A, whereas plasma NA levels after TS were slightly decreased. This finding is in agreement with previous studies, in which we showed that EH patients do not show sympathetic overactivity relevant to cardiovascular autonomic function in resting conditions, but only during sympathetic stress (exercise test, handgrip

samples were always obtained in a highly standardized way at 09.00 h after overnight fasting [9]. The patients were installed in a supine position in a quiet room. An intravenous catheter was placed in an antecubital vein at least 30 min before sampling 10 mL of venous blood. Specimens were immediately sent for processing. Plasma NA and A were determined using a high-performance liquid chromatographic assay [10,11]. The detection limits of this assay were 0.2 nmol L<sup>-1</sup> for NA, and 0.25 nmol L<sup>-1</sup> for A. The reference limits for plasma NA and A were obtained from the literature [12]: the upper limit is 5 nmol L<sup>-1</sup> for NA and 1 nmol L<sup>-1</sup> for A.

Thoracoscopic sympathectomy was performed as described elsewhere [5,13].

Table 1. Plasma noradrenaline (NA) and adrenaline (A) concentrations before and 24 h after thoracoscopic sympathectomy in 13 EH patients

Subject	Sex	Age (years)	NA (ng mL <sup>-1</sup> )		A (ng mL <sup>-1</sup> )	
			Before	After	Before	After
1	F	49	0.18	0.17	0.05	0.05
2	M	15	0.22	0.07	0.07	0.1
3	M	20	0.22	0.08	0.05	0.05
4	M	23	0.27	0.43	0.11	0.1
5	M	21	0.29	0.17	0.05	0.05
6	F	40	0.21	0.26	0.05	0.05
7	M	21	0.74	0.21	0.08	0.05
8	F	25	0.61	0.26	0.05	0.05
9	F	20	0.33	0.14	0.05	0.05
10	M	19	0.14	0.25	0.1	0.17
11	F	25	0.14	0.15	0.1	0.1
12	F	30	0.4	0.22	0.1	0.1
13	F	45	0.59	0.13	0.13	0.1
Mean		27.2	0.33	0.20	0.08	0.08
SD		9.9	0.2	0.09	0.03	0.03
Difference				P = 0.035		P = 0.744



test), and that TS corrects this stress-related sympathetic overactivity [5,6]. In another study [7] we were able to demonstrate that TS in EH patients is associated with a significant decrease in FEF<sub>75</sub> (a parameter of small-airway function), which could be attributed to the sympathetic pulmonary denervation in itself.

NA is a potent agonist of  $\alpha$ - and  $\beta_1$ -adrenergic receptors, and has only a little activity on  $\beta_2$ -adrenergic receptors (10–50 times less than A). As  $\beta$ -receptors on bronchial smooth muscle in humans are exclusively of the  $\beta_2$  subtype [14], the effect of NA on bronchial smooth muscle tone (and, hence, on bronchial airflow) is unmeasurable [15,16]. It is therefore very unlikely that the observed decrease in airflow through small airways that we observed after TS [7] is caused by the observed change in circulating plasma NA. The decrease in circulating NA, however, may reflect the reduced release of NA from the adrenergic sympathetic neurons effected by TS-induced sympathetic interruption. Similarly, the observed postoperative effects on cardiac autonomic activity [5,6] may also be associated with this decrease in circulating plasma NA. Adrenaline, on the other hand, is a powerful bronchodilator through its effect on  $\beta_2$ -adrenergic receptors [15]. As plasma A levels remain unchanged after TS, it is very unlikely that the effects of TS on small-airway function are caused by changes in circulating A. Thus, the observed effects of TS on small-airway function [7] more probably result from a direct partial pulmonary sympathetic denervation effect. These findings, when confirmed, would represent the first evidence of direct functional sympathetic innervation effects on the lung in humans [16].

Post-TS plasma NA and A levels were measured 24 h after the intervention. Postoperative stress, pain and anaesthesia-related factors theoretically might have influenced the results. However, all patients were completely relaxed at the time of the blood sampling, and no patient experienced pain or any other distress at that time. We have previously shown that autonomic hyperactivity in EH patients is only apparent (on the cardiac level at least) after stimulation of the sympathetic system, i.e. after standing or exercise [5,6]. Furthermore, at the palmar level, excessive sweating is mainly exaggerated during exercise and/or emotional stress, and disappears during sympathetic inactivation, e.g. during sleep. It is therefore conceivable that plasma NA (and A) levels *measured during conditions of sympathetic activation* might be abnormally elevated in EH patients before TS, and significantly lowered after TS. Thus, variations in plasma catecholamine levels (i.e. A) could have influenced the measurements of some pulmonary function tests, i.e. FEF<sub>75</sub>, as the performance of forced expiratory manoeuvres itself undoubtedly induces a certain stress to the sympathetic nervous system. Determination of plasma catecholamine levels therefore should also be performed during standardized situations of sympathetic stimulation, e.g. standardized exercise protocols, and during the performance of pulmonary function testing. These studies are planned in the near future. Nevertheless, palmar sweating in EH

patients is almost always—although to a lesser extent than in situations of sympathetic stress—also present at rest [17,18, present observations]. As plasma catecholamine concentrations in this setting were shown to be normal, neuropharmacological factors probably are not—or only to a limited degree—involved in the pathophysiology of EH, at least at resting conditions.

In conclusion, preoperative plasma catecholamine concentrations (NA and A), measured in a standardized way in relaxed, supine subjects, are not elevated in EH patients. D<sub>2</sub>–D<sub>3</sub> thoracoscopic sympathectomy is followed by a decrease in circulating NA, whereas A concentration is unaffected.

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