Exposure to high ambient temperature increases absorption and plasma concentrations of transdermal nicotine

Absorption and plasma concentrations of transdermally delivered drugs may be increased during heat exposure. We studied the effects of short-term heat exposure in a sauna bath on the pharmacokinetics of transdermal nicotine, 25 mg/16 hr, in 12 healthy smokers in an open, randomized crossover study that consisted of a control session and a sauna bathing session. In the sauna session the subjects stayed seated in a sauna bath (mean temperature 82° C (180° F); mean relative humidity 28%) for three 10-minute periods separated by two 5-minute breaks. Sauna bathing significantly ($p < 0.01$ versus control) increased peak plasma concentration, area under the plasma concentration–time curve from 0 to 1 hour, the amount of nicotine absorbed, and the mean plasma nicotine concentrations during heat exposure. No significant difference in nicotine area under the plasma concentration–time curve from 0 to 3 hours was observed. In addition, the combined effects of transdermal nicotine and sauna bathing on hemodynamics, some psychomotor skills, and subjective symptoms were evaluated. We concluded that absorption and plasma concentrations of transdermally delivered nicotine may be increased during exposure to high ambient temperature, probably because of enhanced skin blood flow. However, no adverse symptoms were recorded. (Clin Pharmacol Ther 1996;60:308-15.)

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Heat exposure in the sauna affects sympathetic activity and circulation. Plasma norepinephrine levels are increased during thermal stress, and cutaneous circulation is accelerated as a consequence of blood flow redistribution during intense external heating.[1-4] Acceleration of skin blood flow in the sauna may, in theory, increase the availability of transdermally delivered drugs. Previous studies have shown that during physical exercise, a stress somewhat similar to sauna bathing, plasma concentrations of transdermal glyceryl trinitrate and nicotine are increased.[5-7] Furthermore, similar results have been obtained with transdermal glyceryl trinitrate during external heating and sauna bathing.[6,8]

Nicotine, as a low-molecular weight substance with good lipid and water solubility, can easily be absorbed from skin, and transdermal nicotine replacement therapy is currently being used as an aid in smoking cessation.[9,10] Nicotine has both centrally and peripherally stimulating effects, and nicotine administration has been shown to enhance psychomotor performance and to increase blood pressure, heart rate, and cardiac output.[10-14] Thus possible changes in nicotine plasma levels and pharmacokinetics during sauna bathing may also have clinical relevance for nicotine pharmacodynamics.

Heat exposure and nicotine administration may affect the synthesis of eicosanoids, which are short-living mediators and modulators of many physiologic and pathologic events. Serum levels of vasoconstrictory and proaggregatory thromboxane (TXA_2), measured by its metabolite (TXB_2), have been reported to vary largely during repeated sauna exposure and to decrease in platelet-rich plasma after nicotine stimulation.[15,16] The combined effects

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Supported by Pharmacia AB, Lund, Sweden.
Received for publication Feb. 19, 1996; accepted April 30, 1996.

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0009-9236/96/$5.00 + 0 **13/1/74682**

of nicotine and sauna bathing on serum TXB_2 levels have not been studied, but concomitant nicotine administration and sauna bathing may, in theory, change serum TXB_2 levels and affect platelet aggregation.

The aim of this study was to evaluate the effects of sauna bathing on the pharmacokinetics of transdermally administered nicotine. In addition, some pharmacodynamic tests were performed and plasma norepinephrine and serum TXB_2 levels were measured to get a general view of the combined effects of transdermal nicotine and sauna-induced heat stress on hemodynamics, performance, subjective symptoms, and hormonal responses.

METHODS

Subjects and protocol. Twelve healthy smokers (seven men and five women; age range, 21 to 31 years; weight range, 48 to 88 kg) volunteered for the study. Each subject underwent a physical examination with medical history and laboratory tests (blood count, electrolytes, blood glucose, erythrocyte sedimentation rate, tests for hepatic and renal function, and a 12-lead ECG) before they were accepted for the study. Drug abuse (synthetic and naturally occurring drugs) was excluded by means of urine and blood screening. The laboratory results were all within normal limits, and a summary of the demographic features of the subjects is presented in Table I. All of the subjects had been smoking regularly (≥12 cigarettes a day) for at least 1 year, and their individual cigarette consumption ranged between 12 and 30 cigarettes a day. The Fagerström Tolerance Questionnaire (FTQ), developed originally for assessment of nicotine dependence, was used as an additional screening method of the smoking habits of the subjects.[17] Four of the women used oral contraceptives; the remainder of the subjects did not have medication of any kind for 3 months before or during the study. Further, none of the subjects had participated in other medical trials, donated blood, or been anesthetized during the 3-month period before the study.

The study protocol was approved by the Ethics Committee of the Department of Pharmacology and Toxicology, University of Helsinki. The Ethics Committee consisted of four members, both physicians and laymen, and none of them was personally involved with the study. The subjects gave written informed consent before the study.

The study was carried out at the Department of Pharmacology and Toxicology, Institute of Biomedicine, University of Helsinki. The subjects participated in two open randomized sessions (control and sauna) in a crossover manner. Six of the subjects started the study in a control session and six of them started the study in a sauna session. There was a 1-week washout period between the sessions.

Table I. Some demographic features (mean ± SEM) of the subjects participating in the study (n = 12; seven men and five women)

Age (yr)	25.4 ± 0.9
Weight (kg)	70 ± 4
Body mass index ($kg \cdot m^{-2}$)*	22.8 ± 0.7
Number of cigarettes/day	18 ± 1
Fagerström score	6.0 ± 0.6

*Body mass index = [weight (kg)]/[height (m)]^2.

Drug administration and study design. The subjects were prohibited from smoking and consumption of other nicotine-containing products, alcohol consumption, extensive physical exercise, and sauna bathing for 24 hours before the sessions. On the session days, the subjects were told not to use caffeine-containing drinks (coffee, tea, and cola beverages), chocolate, licorice, or fatty foods for 8 hours before the initiation of the session. The subjects were served a standard breakfast at the study site before the nicotine patches were applied, and eating was not allowed thereafter. Smoking abstinence of the subjects was verified by a carbon monoxide breath tester (Bedfont EC50 Micro Smokerlyzer, Bedfont Scientific Ltd., Kent, England) in which the allowed level of exhaled carbon monoxide was set to be less than 10 ppm. Along with the carbon monoxide screening, breath alcohol concentration (limit ≤0.05%) was also measured (Lion Alcometer S-D2, Lion Laboratories Limited, Barry, England). After the patches were applied, the subjects were allowed to leave the study site, and carbon monoxide and breath alcohol levels were monitored again 4½ hours later, at the beginning of the actual session. After the beginning of the session, the subjects stayed at the study site, were supervised, and were not allowed to leave the department.

Two transdermal nicotine patches (Pharmacia AB, Helsingborg, Sweden)—10 mg/16 hr Nicorette, containing 16.6 mg/20 cm^2 nicotine, and 15 mg/16 hr Nicorette, containing 24.9 mg/30 cm^2 nicotine, were applied by the investigator to a hairless area of the lateral aspect of the right arm of each subject. During the latter session, 1 week later, the patches were applied to the lateral aspect of the left arm of each

subject. The patches were removed 8 hours later (3 hours after the beginning of sauna bathing) and the used patches were attached to a plastic film and stored in their original pouches at +4° C for the analysis of the amount of nicotine that remained in the used patches.

The sauna session consisted of three repetitive 10-minute stays in a sauna bath (mean temperature, 82° C; temperature range, 77 to 84° C; mean relative humidity, 28%; humidity range, 26% to 32%), starting 5 hours after the patches had been applied. The stays in the sauna were separated by two 5-minute breaks in a cooling room at a temperature between 25° C and 27° C. To avoid fluctuations in the temperature and humidity of the steam room during sauna bathing, the subjects were instructed to be seated in the same position in the steam room and they were not allowed to throw water on the stove during the stays in sauna. During the bathing sessions the subjects were allowed to drink tap water ad libitum to avoid excessive dehydration. After finishing the three 10-minute stays in the sauna, and throughout the control session, the subjects were accommodated in a resting room at 23 °C.

Blood sampling and determination of nicotine, norepinephrine, and TXB_2. Venous blood samples for determination of plasma nicotine concentrations were collected in 5 ml heparinized vacuum tubes (Venoject VT-050HL, Terumo Europe N.V., Leuven, Belgium) before the application of the patches (−5 hours), before the beginning of sauna bathing (−30 and −5 minutes) and at 15, 30, 45, 60 minutes and at 1¼, 1½, 1¾, 2, 2¼, 2½, 2¾, and 3 hours after the beginning of sauna bathing. The antecubital veins of the arm opposite from the patches were used for blood sampling. The samples were immediately cooled, and then 20 to 40 minutes after sampling they were centrifuged at 2000 rpm at +4° C for 10 minutes and frozen at −80° C. The samples were taken and were handled by nonsmoking personnel throughout the process to avoid contamination.

Plasma nicotine concentrations were determined with use of a capillary gas chromatography with a nitrogen selective detector.[18] A plasma sample was mixed with 5 mol/L sodium hydroxide and extracted into 1% *n*-butanol in toluene. The sample extract was injected into a capillary gas chromatographic system equipped with a nitrogen-selective detector. The chromatography was performed by a silica capillary column coated with 95% dimethylsilicon and 5% phenylsilicone (CP-Sil 8CB, Chrompack, Middleburg, The Netherlands). Helium was used as the carrier gas, and *N*-methylanabasine was used as an internal standard. The limit of detection was 0.2 $ng \cdot ml^{-1}$ nicotine, and the limit of quantification was 0.6 $ng \cdot ml^{-1}$. The intraday variation, expressed as the coefficient of variation, was less than 16.1% above 2 $ng \cdot ml^{-1}$ and less than 2.3% above 10 $ng \cdot ml^{-1}$. Determination of residual nicotine in the used patches was done by ultraviolet spectrophotometry. The combined laminate was punched and creased, the release liner was removed, and the nicotine of the laminate was extracted into 50 ml *n*-heptane. Nicotine was then extracted into 100 ml of 0.025N hydrochloric acid, and the ultraviolet absorbance of the aliquot and the standard solutions were measured at 259 nm.

Additional samples for plasma norepinephrine and serum TXB_2 analysis were drawn in nonheparinized 10 ml vacuum tubes (Venoject VT-100PXZ, Terumo Europe N.V.) 5 minutes before and ½, 1¼, and 3 hours after the beginning of sauna bathing. Sampling and handling procedures followed the same time schedule in the control session. Samples for TXB_2 analysis were first incubated at +37° C for 30 minutes and then cooled for 5 minutes in an ice container, centrifuged at 2000 rpm for 10 minutes at room temperature (+21° C) and frozen at −20° C. For the assay, the samples were diluted 1:200 in an assay buffer, and TXB_2 concentrations were determined by direct radioimmunoassay with use of ^3H-thromboxane B_2 (Amersham International, Buckinghamshire, England), with double antibody technique as described earlier in the literature.[19] Antiserum was donated by professor C. Taube (Martin Luther University, Halle, Germany). Samples for norepinephrine analysis were immediately cooled, centrifuged at 2000 rpm for 10 minutes at room temperature and stored at −80° C. Plasma norepinephrine was determined by HPLC with electrochemical detection (ESA Coulochem 5100 A, Bedford, Mass.). The method was modified from that described earlier by Seppälä et al.[20] Norepinephrine was extracted with activated alumina (Merck, Darmstadt, Germany), and dihydroxybenzamine (Sigma Chemical Company, St. Louis, Mo.) was used as an internal standard. The aqueous mobile phase contained 0.03 mol/L monochloroacetic acid, 0.03 mol/L trisodium phosphate, 120 $mg \cdot L^{-1}$ octanylsulfonic acid, and 25 $mg \cdot L^{-1}$ sodium ethylenediaminetetraacetic acid (pH 2.55, adjusted with phosphoric acid). A reversed-phase Zorbax octadecylsilane C column (DuPont, Wilmington, Del.) was

used. The intraassay coefficient of variation for norepinephrine assay (2.5 pmol · ml^{-1}) was 5%.

Pharmacokinetic calculations. Mean ± SEM values for nicotine peak plasma concentration (C_{max}, in nanograms per milliliter) were calculated directly from the data. The areas under the plasma concentration versus time curves [AUC(0-1) and AUC(0-3), in nanograms hours per milliliter] were calculated by use of pharmacokinetic software (MK Model version 5.25, Biosoft, Cambridge, England). The zero time point for AUC calculations was the beginning of heat exposure, 5 hours after the patches were applied. The amount of nicotine absorbed from the patches (in milligrams) was calculated as the difference between the labeled amount of nicotine (in milligrams) in the patches and the residual amount of nicotine remaining in the patches (in milligrams) after their removal.

Pharmacodynamic measurements. The time schedule of pharmacodynamic measurements was identical during the control session and during the sauna session. Blood pressure and heart rate were measured by an oscillometric digital blood pressure monitor (Omron HEM-405C, Omron Corporation, Tokyo, Japan), while the subjects were supine, 15 minutes before and at 10 and 50 minutes, 1 hour and 35 minutes, and 3 hours after the beginning of the control and sauna sessions. Psychomotor skills were measured by tests currently used in our laboratory.[21-23] The subjects were pretrained for the tests to minimize learning effects during the sessions. The tests included the critical flicker fusion frequency (CFF) by a red light-emitting diode from 1 meter distance with fixed pupilla diameter to measure the overall integrative activity and arousal of the subjects, expressed in hertz, and the Digit Symbol Substitution Test (DSST) for 2 minutes to measure sensory processing performance and concentration ability. The DSST was performed 20 minutes before and at 25 and 50 minutes, 1 hour and 35 minutes, and 3 hours after the beginning of the session. The CFF was performed 20 minutes before and at 50 minutes, 1 hour and 35 minutes, and 3 hours after the beginning of the session. Along with the DSST, the subjects evaluated their subjective symptoms with visual analog scales (VAS), 100 mm long unscaled horizontal lines that consisted of the following pairs of adjectives at the extremes of the lines, both in Finnish and in English: alert/drowsy, clumsy/skillful, mentally slow/quick-witted, dizziness/feeling stable, calm/nervous, very good/very bad performance.

Statistical analysis. The amount of subjects needed for the study was calculated by power analysis. The difference expected to detect in mean plasma nicotine concentrations was ±8 ng · ml^{-1} (SD ± 4.5 ng · ml^{-1}) at a significance level of $p < 0.05$ (power 0.80).

Mean ± SEM values for pharmacodynamic data were calculated for the absolute values and for the changes from respective baseline (Δ values). The absolute values of plasma nicotine concentrations, pharmacokinetic parameters, plasma norepinephrine, and TXB_2 were first treated with two-way ANOVA (treatment × week), and then compared by the two-sided Wilcoxon signed-rank test. The baseline values of the pharmacodynamic data were analyzed by two-way ANOVA (treatment × week). The comparisons of the treatments (control versus sauna) were then made by comparing the Δ values with two-way ANOVA, followed by two-sided Wilcoxon signed-rank test. Within-group comparisons (versus respective baseline) of the data were performed by Wilcoxon signed-rank test. Nicotine plasma concentrations of the oral contraceptive users ($n = 4$) versus the remainder of the subjects ($n = 8$) were compared by t test for independent samples. The level of statistical significance was set at $p < 0.05$, and all the calculations were made by statistical software (Systat 4.0, Systat Inc., Evanston, Ill.).

RESULTS

Plasma nicotine concentrations and pharmacokinetics. Mean plasma nicotine concentrations were significantly increased ($p < 0.01$ versus control, Wilcoxon) 15, 30, 45, and 60 minutes after the beginning of heat exposure in the sauna (Fig. 1). Further, C_{max} and the amount of nicotine absorbed were significantly ($p < 0.01$ versus control, Wilcoxon) increased in the sauna session (Table II). No difference in nicotine AUC(0-3) was observed, but AUC(0-1) was significantly higher ($p < 0.01$ versus control, Wilcoxon) in the sauna session (Table II). Plasma nicotine concentrations of oral contraceptive users ($n = 4$) versus the remainder of the subjects ($n = 8$) were analogous in the control session and in the sauna bathing session.

Plasma norepinephrine and serum TXB_2. Plasma norepinephrine was increased ($p < 0.05$; Table III) at 30 minutes compared with the baseline value. No changes in serum TXB_2 levels were observed (Table III). In addition, there were no differences in norepinephrine and TXB_2 values between the sessions.

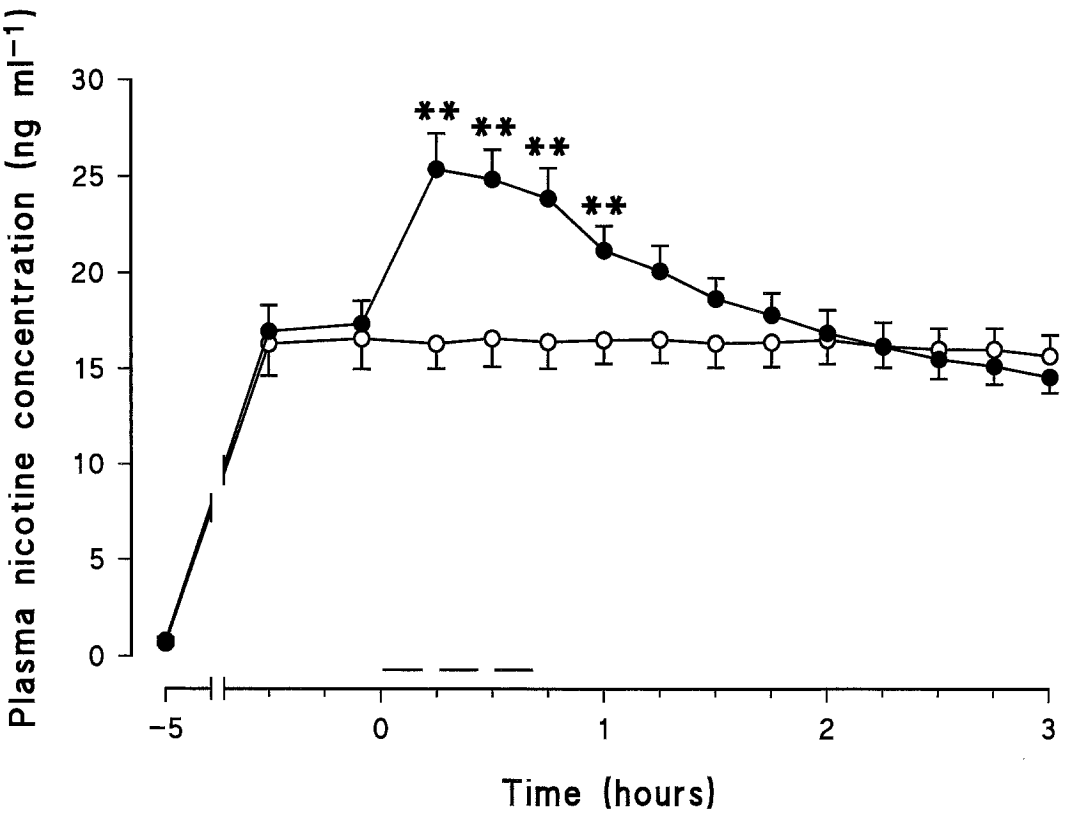

Fig. 1. Plasma nicotine concentrations (mean ± SEM) with the nicotine patches (25 mg/16 hr) in the control session *(open circles)* and in the sauna bathing session *(solid circles); n* = 12 in both sessions. The *horizontal lines* indicate the 10-minute stays in the sauna during the sauna bathing session. $^{**}p < 0.01$ versus control, Wilcoxon signed-rank test.

Table II. Pharmacokinetic parameters (mean ± SEM) of transdermal nicotine, 25 mg/16 hr, in the control session and in the sauna bathing session (n = 12 in both sessions)

	Control	*Sauna*
C_{max} (ng · ml^{-1})	18.0 ± 1.4	26.1 ± 1.8*
Amount absorbed (mg)	15.9 ± 0.3	17.2 ± 0.4*
AUC(0-1) (ng · hr · ml^{-1})	17.8 ± 1.5	25.1 ± 1.6*
AUC(0-3) (ng · hr · ml^{-1})	50.3 ± 3.9	59.6 ± 3.6

C_{max}, Peak plasma concentration; AUC(0-1), area under the plasma concentration–time curve from 0 to 1 hour; AUC(0-3), AUC from 0 to 3 hours.
*$p < 0.01$ versus control, Wilcoxon signed-rank test.

Pharmacodynamics. Systolic blood pressure and heart rate were significantly increased at 10 minutes in the sauna session ($p < 0.01$ versus control; Fig. 2). No changes in diastolic blood pressure were observed. The subjective VAS evaluation revealed increased nervousness and impairment of performance during sauna bathing (Table IV). There were no differences in the DSST and CFF between the sessions (Table IV).

DISCUSSION

It has been suggested that the changes in bioavailability and plasma concentrations of transdermally administered drugs during exercise and heat exposure are related to an increase in local blood flow of skin area.[5-8] This hypothesis is further supported by our results, because heat exposure during transdermal nicotine administration increased the plasma concentrations and the absorbed amount of nicotine. On the basis of our results, local blood flow may be the rate-limiting step in the absorption of nicotine and other absorbable drugs from transdermal drug delivery systems into systemic circulation. It is still unclear whether the basic mechanism for the changes observed was increased absorption of nicotine from the patches or enhanced transporta-

Table III. Plasma norepinephrine and serum thromboxane B_2 concentrations (mean ± SEM) in the control session and in the sauna bathing session (n = 12)

	Control	*Sauna*
Norepinephrine (pmol · ml^{-1})		
Baseline	2.0 ± 0.6	1.2 ± 0.5
30 min	1.4 ± 0.4	2.2 ± 0.5*
1¼ hr	1.2 ± 0.4	2.3 ± 0.7
3 hr	1.1 ± 0.2	1.6 ± 0.4
Thromboxane B_2 (ng · ml^{-1})		
Baseline	163 ± 10	143 ± 16
30 min	172 ± 15	157 ± 15
1¼ hr	142 ± 9	148 ± 16
3 hr	156 ± 13	136 ± 18

*$p < 0.05$ versus respective baseline, Wilcoxon signed-rank test. No differences between the control and sauna sessions were observed.

tion of nicotine from a subcutaneous tissues into systemic circulation. Changes in the physicochemical properties of the patch also cannot be totally excluded, but they seem quite unlikely because after the sauna bathing, nicotine concentrations returned to the presauna levels, implying that nicotine-releasing properties of the patch were unaffected.

Intravenously administered nicotine has been shown to retard the absorption of transdermal nicotine, probably in relation to local vasoconstriction induced by nicotine itself.[24] Thus it seems that heat-induced local vasodilatation during sauna bathing is even more pronounced than the vasoconstrictory effects of nicotine, because the effects of external heating on nicotine plasma levels were very rapid and clear. Plasma nicotine concentration had already reached its peak after the first 10-minute stay in the sauna, and the plasma levels remained elevated throughout the heat exposure, gradually returning to the presauna levels after the cessation of external heating. As could be expected on the basis of nicotine plasma concentration data, AUC(0-1) was significantly increased during sauna bathing, but the difference between the sauna session and the control session subsided toward the end of the sampling period and no differences between the AUC(0-3) values were observed.

Both sauna bathing and nicotine administration can increase blood pressure and heart rate.[1,13,14,25] During the control session no changes in hemodynamics were observed, but during the sauna bathing session both systolic blood pressure and heart rate were significantly increased. In addition, plasma

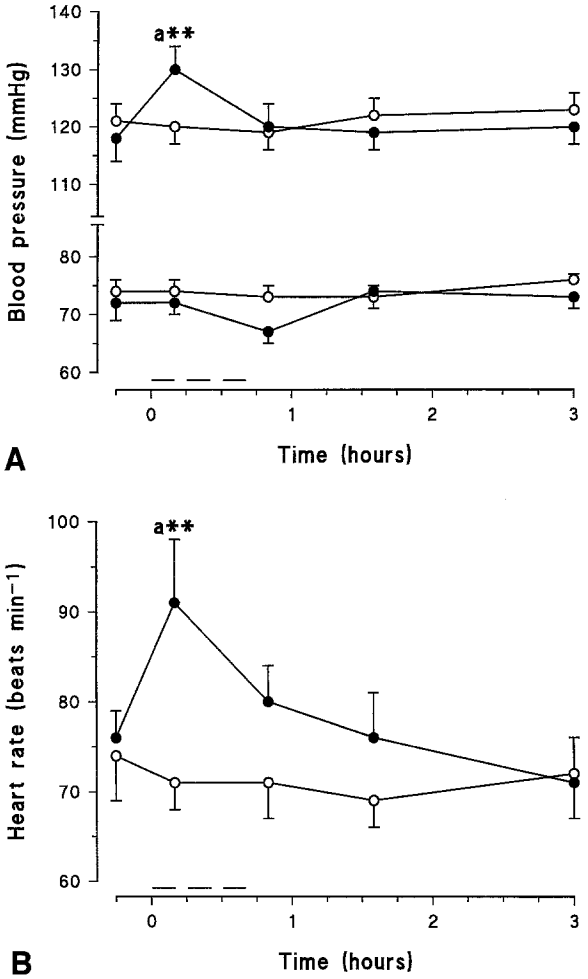

Fig. 2. Blood pressure and heart rate during use of the nicotine patches (25 mg/16 hr). **A,** Systolic *(upper lines)* and diastolic *(lower lines)* blood pressure (mean ± SEM) in the control session *(open circles)* and in the sauna bathing session *(solid circles)*. **B,** Heart rate (mean ± SEM) in the control session *(open circles)* and in the sauna bathing session *(solid circles)*. The *horizontal lines* indicate the 10-minute stays in the sauna during the sauna bathing session. **$p < 0.01$ versus Δ control; $^a p < 0.01$ versus respective baseline, Wilcoxon signed-rank test; n = 12 in both sessions.

norepinephrine levels were elevated during sauna bathing, and consequently the changes in blood pressure and heart rate can mainly be explained by heat stress–induced increase in sympathetic activity. The fact that the hemodynamic responses were abolished 5 minutes after the end of the third 10-minute stay in the sauna, even though plasma nicotine levels were still elevated, further supports the

Table IV. Pharmacodynamic results (mean ± SEM) in the control session and in the sauna session (n = 12)

	Control	*Sauna*
DSST/2 min		
Baseline	97 ± 3	97 ± 4
25 min	101 ± 4	102 ± 3
50 min	101 ± 4*	102 ± 2*
1 hr 35 min	101 ± 4	103 ± 3†
3 hr	100 ± 3*	100 ± 3
CFF (Hz)		
Baseline	22.1 ± 0.5	21.7 ± 0.6
50 min	21.7 ± 0.5	22.1 ± 0.5
1 hr, 35 min	22.0 ± 0.6	22.1 ± 0.6
3 hr	21.8 ± 0.5	21.8 ± 0.6
VAS calm/nervous (mm)		
Baseline	25 ± 8	15 ± 4
25 min	19 ± 5	37 ± 7*‡
50 min	19 ± 4	25 ± 5*
1 hr, 35 min	16 ± 3	17 ± 3
3 hr	17 ± 3	25 ± 6
VAS good/bad performance (mm)		
Baseline	32 ± 5	26 ± 3
25 min	28 ± 3	43 ± 5†‡
50 min	34 ± 6	38 ± 5
1 hr, 35 min	30 ± 4	32 ± 4
3 hr	29 ± 4	35 ± 5

DSST, digit symbol substitution test; CFF, critical flicker fusion; VAS, visual analog scale.
*$p < 0.05$; †$p < 0.01$ versus respective baseline; ‡$p < 0.05$ versus Δ control; Wilcoxon signed-rank test.

primary role of increased sympathetic activity in the hemodynamic effects observed. Nevertheless, it must also be noted that the cardiovascular effects of nicotine have been reported to reach a plateau during continuous nicotine administration, probably due to acute tolerance.[13,26] Because a sauna session with placebo was not included in the study protocol, the individual contribution of nicotine administration or heat exposure to blood pressure and heart rate responses during sauna bathing could not be differentiated.

Nicotine administration has also been reported to improve CFF threshold and motor reactions.[11] In our design, CFF and DSST did not differ between the sessions, despite the higher nicotine concentrations during the sauna bathing session. Slight improvement in both sessions, when compared to respective baseline values, was seen in DSST performance, and it might be explained by learning effect, even though the subjects were pretrained for the psychomotor tests. In addition, when psychomotor testing was performed, adequate plasma nicotine concentrations had already been reached, and a recovery effect from a state of nicotine abstinence as a performance-improving factor can thus be outruled. Moreover, the subjects reported nervousness and impaired performance during the sauna session, but despite subjective discomfort, DSST performance was improved compared with the baseline performance.

No changes in serum TXB_2 levels were observed, and the finding was in line with the results of a previous study performed during sauna bathing.[15] During physical exercise the serum levels of TXB_2 have been reported to increase, but sauna bathing–induced stress seems to be somewhat milder than that of physical exercise, and in the present study sauna bathing did not enhance the production of TXB_2.[27] It is concluded that the combined effects of transdermal nicotine and sauna bathing on serum TXB_2 levels are negligible.

In conclusion, heat exposure in the sauna increased total absorption of transdermal nicotine and transiently increased plasma nicotine concentrations. It is suggested that increased nicotine absorption and higher plasma concentrations resulted from increased cutaneous blood flow during heat exposure. Moreover, systolic blood pressure and heart rate were increased in the sauna session during heat exposure. The results may have clinical relevance for exposure to high ambient temperature during high-dose nicotine replacement therapy, especially for persons with cardiovascular diseases.

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