Effects of Transdermal Nicotine Patches on Energy Expenditure Measured with a Human Calorimeter

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Objective: Previous studies investigating the link between nicotine and energy expenditure (EE) have shown a 6–10% increase in EE after nicotine intake using gum or spray, which increase blood level acutely. However, the effects of transdermal nicotine patches, which increase nicotine blood levels gradually, are still unknown. Thus, we studied the effects of nicotine patches on EE using human calorimeter.

Design: EE was measured over a 10-hour period with a human calorimeter using a crossover design to assess whether transdermal nicotine patches increase EE. Subjects were 8 adult, male non-smokers.

Interventions: All subjects followed the same schedule for measurement: enter the human calorimeter at 6:45 PM, sleep from 11:00 PM to 6:00 AM, and rest on a chair from 6:00 AM to 7:00 AM. EE and Respiratory quotient (RQ) were calculated from measurements from the human calorimeter.

Results: There were no significant differences in EE during the sleeping period between experimental and control conditions (Nicotine: 1.08 ± 0.08 kcal/min, Control: 1.06 ± 0.08 kcal/min; $p = 0.161$). EE while sitting at rest 10 h after nicotine patch application was significantly increased by 0.07 kcal/min (5.8%) in the nicotine condition compared to the control condition (Nicotine: 1.22 ± 0.10 kcal/min, Control: 1.15 ± 0.12 kcal/min; $p = 0.035$).

Conclusion: Results from this study indicate that EE may increase after transdermal nicotine patch exposure when blood nicotine levels have reached an estimated maximum.

Key words: resting energy expenditure, human calorimeter, nicotine replacement therapy

Introduction

Smoking is a major cause of cancer, cardiovascular diseases, diabetes, and many other diseases. Smoking is also the second leading risk factor for global all-cause mortality after hypertension¹⁾. Therefore, prevention of passive smoking and providing smoking cessation programs are essential for improving public health. The World Health Organization has set a goal of reducing the global smoking rate by 30% by 2025²⁾. However, many

smokers attempting to quit smoking experience nicotine withdrawal symptoms, such as cravings, anxiety, irritability, and depression, in the early stages of cessation. Many smokers relapse when attempting to quit because of these symptoms. In recent years, nicotine replacement therapy, in which nicotine is administered in the form of a patch or chewing gum to relieve withdrawal symptoms and urges, has been broadly used as an effective means to support smoking cessation efforts³⁾.

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[Received Dec. 9, 2015] [Accepted Mar. 10, 2016]

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doi: 10.14789/jmj.62.232

Cardiovascular risks are greatly reduced for those who succeed in smoking cessation⁴⁾; however, successful smoking cessation is often accompanied by weight gain⁵⁻⁷⁾, which is also a known risk factor for cardiovascular disease. Aubin *et al.*⁸⁾ conducted a meta-analysis that showed participants experienced a 4–5 kg increase in body weight in the year following successful smoking cessation. Hofstetter *et al.*⁹⁾ compared 24-hour energy expenditure (EE) in smokers with a human calorimeter and reported a 200 kcal increase in EE on the day subjects smoked every 30 minutes compared to a day without smoking. Therefore, post-smoking cessation weight gain, which is also a public health issue, is considered to be a phenomenon related to the pharmacological effect of nicotine on EE.

Previous studies investigating the link between nicotine replacement therapy, in gum or spray form, and EE have shown a 6–10% increase in EE immediately after nicotine intake¹⁰⁻¹³⁾. However, some of these studies¹⁰⁻¹²⁾ were based on respiration mask measurements over the short term. In addition, the effects observed were measured after a short period of non-smoking, from several hours to overnight. Thus, possible effects on EE from nicotine withdrawal, such as smoking urges and other non-nicotine factors associated with temporary smoking cessation, cannot be ruled out. In the present study, we studied the effects of transdermal nicotine patches on EE measured over a 10-hour period with a human calorimeter in non-smokers who had no nicotine withdrawal symptoms or urges.

Materials and methods

1. Subjects

This study included 10 adult male non-smokers aged 23 to 28 years old. Prior to the study, all subjects provided written consent to participate after receiving information on risks and adverse effects associated with nicotine patch application. Although none of the subjects in this study encountered any adverse effects from the nicotine patches during pre-screening, 2 of the 10 subjects reported headaches, nausea, and other symptoms after waking following nicotine patch application in the main study, and were thus excluded from analysis. Total subject count for analysis was 8. The study protocol was approved by the Research Ethics Review Board of the Juntendo University

Graduate School of Health and Sports Science (Tokyo, Japan).

2. Study design

We used a crossover experimental design; initial conditions were determined randomly for each subject. Subject EE was measured twice: once when a nicotine patch was applied to subjects (nicotine condition), and once with placebo patches (control condition). Both measurements were conducted within a period of 7–10 days, and all subjects completed calorimetry measurements between early August and mid-September of 2013.

3. Energy expenditure measurements

Energy expenditure was measured with a human calorimeter (FHC-20S, Fuji Medical Science) from 6:30 PM to 8:15 AM the next morning. A human calorimeter is a piece of equipment used to measure EE indirectly from oxygen uptake (VO_2) and carbon dioxide production (VCO_2) volumes in a hermetically-sealed room in which a subject can live normally for several hours to days. The human calorimeter used in this study had an internal volume of 19,000 L and facilities (e.g., bed, toilet, desk, chair, television and phone). Temperature and humidity of the internal atmosphere were adjusted to 25°C and 55%, respectively. With an exhaust flow rate of 100 L/min, O_2 and CO_2 exhaust concentrations were measured every 15 s with a mass spectrometer and used to calculate VO_2 and VCO_2 per min based on Henning's formula¹⁴⁾. The EE was calculated by applying the resulting VO_2 and VCO_2 to Weir's formula¹⁵⁾. The resulting EE values, adjusted for a 2-min time lag, were used for data analyses. Alcohol combustion tests (7-h combustion) indicated theoretical recoveries of O_2 , CO_2 , and respiratory quotient (RQ) of, respectively, 101.4%, 101.5% and 100.0% before the study and 99.4%, 100.5% and 101.1% after the study. These results guaranteed accurate calorimetry measurements. Prior to the study, all subjects stayed in the human calorimeter at least once with a schedule similar to the one used in the actual experiment to acclimatize to the living environment.

The experimental schedule set for all subjects is shown in Table-1. The subjects in this study refrained from any strenuous physical activity, including general exercise, from the day before

Table-1 Time schedule in the human calorimeter

Time	Activity
6:30 PM	Enter the calorimeter
6:30 PM–7:00 PM	Sitting, reading, or watching TV
7:00 PM–7:15 PM	Dinner
7:15 PM–11:00 PM	Desk work or watching TV
9:00 PM	Nicotine patch application
11:00 PM	Sleep
6:00 AM	Wake up (go to the toilet)
6:00 AM–7:00 AM	Sitting (TV watching only)
7:00 AM–8:00 AM	Sitting, reading, or watching TV
8:15 AM	Exit the calorimeter

measurements began; fasted (but were allowed water) beginning at 3:00 PM on the day of measurement; and arrived at the laboratory to begin the experiment at 6:00 PM. The subjects then underwent height and weight measurements, wore electrodes for electrocardiography, and entered the human calorimeter at 6:30 PM. The subjects stayed in the human calorimeter for 13 h and 45 min, exiting at 8:15 AM the next morning.

Regarding activities in the human calorimeter, the subjects were instructed as follows:

- 1) From the time of entrance to 11:00 PM, subjects were not allowed to exercise or lie in bed, and passed time by sitting on a chair and watching television or working on a computer, except while using the toilet.
- 2) At 7:00 PM, subjects were given a meal provided by the examiner in the human calorimeter. The contents of the meal were identical for the nicotine and control conditions for each subject.
- 3) The subjects slept from 11:00 PM to 6:00 AM.
- 4) Upon waking at 6:00 AM, subjects sat on a chair immediately after defecation/urination and remained in a resting state while in a sitting posture for 1 h while watching television until 7:00 AM.
- 5) The subjects passed time by sitting on a chair and watching television or working on a computer from 7:00–8:15 AM, after which they exited the calorimeter.

Adherence to instructions was checked by visually inspecting the subjects on a regular basis and confirmed with the subjects in writing after exiting the calorimeter. Subjects' heart rates (beats per

minute, bpm) were recorded throughout their entire stay in the human calorimeter with an electrocardiograph (DS-7520, Fukuda Denshi). Body fat percentage and skeletal muscle mass were estimated using the impedance method (Inbody 730, Biospace). EE and RQ were calculated from measurements in the human calorimeter.

4. Nicotine patches

In this study, nicotine patches were used to assess the pharmacological effects of nicotine from nicotine replacement therapy on EE. Since blood nicotine levels are estimated to peak 8–10 h after nicotine patch application¹⁶⁾, a nicotine patch (Nicotinell 20, 20 cm², 35 mg/24 h) was applied to the left arm of each subject in the nicotine condition at 9:00 PM to obtain the highest blood nicotine level at 6:00 AM when the subject awoke. Meanwhile, a patch devoid of nicotine was applied to the left arm of each subject in the control condition at 9:00 PM. Because headaches and nausea can be caused by nicotine patch application and could affect study results, candidate subjects underwent pre-screening, wherein patches with a lower nicotine content were tested on the subjects for 10 h prior to the study; only those who did not experience adverse effects, such as headaches and nausea, were included.

5. Statistical analyses

Microsoft Office Excel 2008 and PASW Statistics 17.0 were used for data processing and statistical analyses, respectively. All variable results are presented as mean $\pm$ standard deviation. All data obtained every hour from 9:00 PM to 7:00 AM were averaged. Statistical analyses were performed using a two-way analysis of variance (ANOVA) with repeated measures to evaluate the effect of the nicotine patch on EE (Condition $\times$ Time). Statistical significance level was set at 0.05.

Results

Characteristics and body composition of included subjects are shown in Table-2. Mean age and body mass index were 26.3 ± 1.7 years and 22.2 ± 1.6 kg/m², respectively.

Table-3 and Figure-1 show changes in EE while the subjects were in the human calorimeter. There was a significant main effect of time but no

Table-2 Subjects' characteristics (n=8)

Variables	Age (y)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Muscle mass (kg)	Body fat mass (kg)	% Body fat (%)
Mean	26.3	173.0	66.6	22.6	31.7	10.5	15.8
SD	1.7	5.7	6.8	1.6	3.4	1.9	1.8

Table-3 Energy expenditure during stay in the human calorimeter (n=8)

Time	Nicotine (kcal/min)	Control (kcal/min)	p value
Awake 9:00 PM-11:00 PM	1.41 ± 0.11	1.41 ± 0.13	0.888
Sleeping 11:00 PM-6:00 AM	1.08 ± 0.08	1.06 ± 0.08	0.161
Sitting 6:00 AM-7:00 AM	1.22 ± 0.10	1.15 ± 0.12	0.035
Overall 9:00 PM-7:00 AM	1.16 ± 0.03	1.14 ± 0.09	0.262

Figure-1 Mean hourly energy expenditure (EE) in the human calorimeter for nicotine (◆) and control (○) conditions. Significant differences (*) was observed at 6:00-7:00 AM when subjects were sitting (p=0.035).

significant main effect of condition and interactions in EE. Total EE during sleeping period from 9:00 PM to 6:00 AM the next morning in the nicotine condition was 1.08 ± 0.08 kcal/min, which was not significantly different from the control condition total of 1.06 ± 0.08 kcal/min (p=0.161). The mean EE in the nicotine condition was significantly greater than the control condition only when subjects were sitting at rest (6:00-7:00 AM) (nicotine, 1.22 ± 0.10 kcal/min, control, 1.15 ± 0.12 kcal/min; p=0.035, Figure-1). At this time, blood

nicotine levels had presumably reached their peak.

The mean heart rate during the nicotine condition tended to be higher than during the control condition while subjects were sleeping (11:00 PM to 6:00 AM the next morning) (nicotine: 52.3 ± 7.1 bpm, control: 49.9 ± 6.3 bpm; p=0.068, Table-4). During the resting hour after waking (6:00-7:00 AM), the mean heart rate was significantly higher in the nicotine condition than that in the control condition (nicotine: 63.7 ± 8.2 bpm, control: 56.9 ± 7.3 bpm; p=0.011, Figure-2).

Table-4 Heart rate during stay in the human calorimeter (n=8)

Time	Nicotine (bpm)	Control (bpm)	p value
Awaking 9:00 PM–11:00 PM	60.6 ± 6.4	60.7 ± 7.0	0.888
Sleeping 11:00 PM–6:00 AM	52.3 ± 7.1	49.9 ± 6.3	0.068
Sitting 6:00 AM–7:00 AM	63.7 ± 8.2	56.9 ± 7.3	0.011
Total 9:00 PM–7:00 AM	55.0 ± 6.5	52.7 ± 5.9	0.068

Figure-2 Mean hourly heart rate in the human calorimeter for nicotine (◆) and control (○) conditions. Significant differences (*) was observed at 5:00–6:00 AM when subjects were sleeping ($p=0.017$) and 6:00–7:00 AM when subjects were sitting ($p=0.011$).

The mean RQ in the nicotine condition was higher than in the control condition during sleeping (11:00 PM to 6:00 AM the next morning) (nicotine: 0.88 ± 0.03 , control: 0.85 ± 0.01 ; $p=0.035$) and sitting at rest (6:00–7:00 AM) (nicotine, 0.91 ± 0.05 , control, 0.87 ± 0.02 ; $p=0.035$, Table-5, Figure-3). And, total RQ from 9:00 PM to 7:00 AM the next morning in the nicotine condition was significantly higher (nicotine, 0.89 ± 0.03 , control, 0.86 ± 0.02 ; $p=0.035$).

Discussion

In this study, we investigated the effects of nicotine patch use on EE in non-smokers using a randomized crossover experimental design to

assess whether transdermal nicotine patches increase EE measured over a 10-hour period with a human calorimeter. A distinguishing feature of this study is that although there were no significant differences in EE during sleep between the nicotine patch condition and the non-nicotine patch (control) condition, EE while sitting at rest 10 h after nicotine patch application was significantly increased by 0.07 kcal/min (5.8%) in the nicotine condition compared to the control condition.

Since Dill *et al.*¹⁷⁾ and Hiestand *et al.*¹⁸⁾ reported increased EE in a resting state immediately after consuming a single cigarette, a number of studies have demonstrated that EE increases after various manners of nicotine intake, including smoking⁹⁻¹³⁾.

Table-5 Respiratory quotient during staying human calorimeter (n=8)

Time	Nicotine	Control	p value
Awaking 9:00 PM-11:00 PM	0.90 ± 0.03	0.91 ± 0.03	0.779
Sleeping 11:00 PM-6:00 AM	0.88 ± 0.03	0.85 ± 0.01	0.035
Sitting 6:00 AM-7:00 AM	0.91 ± 0.05	0.87 ± 0.02	0.035
Total 9:00 PM-7:00 AM	0.89 ± 0.03	0.86 ± 0.02	0.035

Figure-3 Mean hourly respiratory quotient (RQ) in the human calorimeter for nicotine (◆) and control (○) conditions. * Significant difference was observed at 3:00-4:00 AM, 4:00-5:00 AM, and 5:00-6:00 AM when subjects were sleeping and 6:00-7:00 AM when subjects were sitting ($p < 0.05$).

Hofstetter *et al.*⁹⁾ measured total EE over 24 h using a human calorimeter for subjects; when comparing the experimental condition of smoking (24 cigarettes per day) to the control condition (no smoking), 24-hour EE for the smoking condition was greater than that for the control (+9.6%), with an approximate difference of 200 kcal (smoking: $2,445 \pm 120$ kcal, control: $2,230 \pm 115$ kcal; $p < 0.001$). The nicotine-induced increase in EE was attributable to the pharmacological effects of nicotine, including stimulation of the sympathetic and parasympathetic nervous systems and secretion of catecholamines (adrenaline and noradrenaline)^{19) 20)}. Although nicotine concentration in the blood was not measured in the current study, it has been

reported that blood nicotine concentrations reach a maximum level 10 h after application of a nicotine patch similar to the one used in our study¹⁶⁾. While EE was not significantly different for the nicotine and control conditions in the observed period between 9:00 PM to 6:00 AM, EE was significantly increased by 0.07 kcal/min (5.8%) for the nicotine condition at rest 10 h after nicotine patch application. This confirmed that EE increased when blood nicotine levels were estimated to be sufficiently high (Table-3). In addition, a previous study showed that nicotine patches induce a 6-10 bpm heart rate increase that occurs at least 7 h after application²¹⁾. In our study, the mean heart rate while sitting at rest 10 h after nicotine patch

application was significantly increased by 6.9 bpm in the nicotine condition compared to the control condition (Table-4). These results suggest that elevated nicotine concentrations in the blood and associated increases in heart rate may underlie the increased EE during the observed sitting period.

Our results showed an increase in RQ with transdermal nicotine patch application which means increased in the amount of carbohydrate oxidized. The increase in RQ with transdermal nicotine patch application might be explained by effects of nicotine, including stimulation of the sympathetic and parasympathetic nervous systems and secretion of catecholamines (adrenaline and noradrenaline)^{19) 20)}. Interestingly, in our study, the mean heart rate in nicotine condition was higher than control condition. Hofstetter *et al.*⁹⁾ reported that RQ during sleeping after smoking 24 cigarettes per day was elevated slightly and attributed this change to an increase in heart rate. Our results that an increase HR with transdermal nicotine patch application is consistent with their results. However, there is still scientific disagreement on the effects of nicotine on RQ. Perkins *et al.*¹⁰⁾ reported that RQ decreased with nicotine spray, but Jessen *et al.*¹²⁾ found no significant change in RQ with nicotine gum. Concerning the effects of nicotine on RQ, further research is needed.

This study also has some limitations. First, we could not address possible differences in response to nicotine among the study subjects. Considering that two subjects had symptoms such as nausea when they awoke, it is plausible that nicotine responsiveness varied substantially from one individual to another. In a previous study reporting nicotine-induced increases in EE, some subjects showed unchanged or decreased EE after nicotine application²²⁾. And, unlike previous studies, our study was conducted with non-smokers; this allowed us to evaluate the effects of a transdermal nicotine patch on EE without any interference from nicotine withdrawal symptoms, smoking urges, and/or other non-nicotine factors associated with smokers who temporarily stop smoking. Therefore, it is unclear our findings may apply to current smokers. Future studies should be designed to consider the potential variation in nicotine responsiveness between individuals and be recruit smokers. Second, the study subjects exited the human

calorimeter at 8:15 AM the following day, and changes in EE after that time were not investigated. Since most daily physical activities are non-exercise activity thermogenesis (NEAT) activities²³⁾, such as maintaining posture (sitting or standing) and fidgeting, the nicotine patch-induced increase in EE might have been masked by those activities. Further studies are necessary to determine the effects of nicotine replacement therapy on the total amount of daily EE, including diet and physical activity. Third, transdermal nicotine patches were applied to each subject in the nicotine condition at 9:00 PM to obtain the highest blood nicotine level at next morning, yet nicotine patch users in non-experimental conditions tend to apply a new patch in the morning. Although it has been suggested that use of the patch overnight could induce sleep disturbances, such as unpleasant or strange dreams²⁴⁾, we did not measure adverse effects on sleep or polysomnographic measures of sleep quality. Thus, future studies should investigate EE during the morning combined with assessing adverse effects of overnight transdermal nicotine patch use. Finally, the fact that all study subjects were male represents another limitation given the possible differences in nicotine responsiveness between males and females. Lower smoking cessation success rates and greater increases in body weight have been reported for women undergoing nicotine replacement therapy compared with males undergoing the same treatment²⁵⁾. These gender differences warrant further studies on the effects of nicotine replacement therapy on EE in a population including both men and women.

Our results that EE with nicotine patches increased by 5.8% 10 h post-application is important in clinical setting. Assuming that a nicotine patch is continuously applied and supplies nicotine sufficient to maintain the highest possible blood level for 12 h, the expected increase in EE is 50–60 kcal, higher-dose transdermal nicotine patch may increase EE more. However, nicotine replacement therapy is used to gradually decrease the nicotine concentration (content) over time to achieve successful smoking cessation, the EE increase from the pharmacological effects of nicotine may be decreased as nicotine replacement therapy advances. Therefore, programs and information for prevention of weight gain, such as avoiding overeating

and increasing physical activity will be suggested, even when smoking cessation is attempted with the aid of nicotine replacement therapy.

In conclusion, our study provides novel information on the effects of transdermal nicotine patches on increasing EE when blood nicotine levels have reached an estimated maximum and indicates that they may have null effects for preventing weight gain during smoking cessation.

Acknowledgments: We wish to thank all of the participants in our study.

Ethical approval

The Research Ethics Review Board of the Juntendo University Graduate School of Health and Sports Science (Tokyo, Japan) approved this study.

Funding

This work was supported in part by a collaborative research grant from the Juntendo University Graduate School of Health and Sports Science and Institute of Health and Sports Science & Medicine.

Conflict of interests

None of the authors have any competing interests to disclose.

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