SKIN BLOOD FLOW RESPONSES AND FOREARM REACTIVE HYPEREMIA AFTER NIACIN INGESTION

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Skin blood flow and core temperature were measured before and after niacin ingestion in eight subjects. Each subject was tested on two occasions in climatic conditions of 30°C with moderate humidity. Following niacin ingestion, peak forearm blood flow (FBF) by venous occlusion plethysmography averaged 8.0 (1.7) ml/100 ml/min from an average baseline of 2.2 (0.5) ml/100 ml/min, an increase of 265%. Forearm skin blood flow (laser doppler flowmetry, LDF) increased 310% (83) at peak niacin vasodilation to 13.1 (4.1) ml/100 ml/min from the baseline of 3.4 (1.4) ml/100 ml/min. Chest skin blood flow (LDF) increased 550% (154) compared to baseline. Higher skin blood flow significantly increased heat loss from the skin decreasing core temperature an average of 0.44°C (0.10) after niacin ingestion. Reactive hyperemia measured by laser doppler flowmetry in forearm skin upon the release of brachial arterial occlusion averaged 11.9 (1.7) ml/100 ml/min, an increase of 250(110)% above control blood flow. This hyperemic response was 12% less than peak skin blood flow observed during the maximal niacin effect. Nicotinic acid, increased skin blood flow, increased skin temperature and decreased core temperature as we reported previously. Although widespread skin vasodilation occurred in most subjects, the extent of the vasodilation and the intensity of subjective symptoms varied within and between individuals.
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EXECUTIVE SUMMARY

Oral niacin ingestion increases skin blood flow at rest and during exercise. Since increases in skin blood flow raise skin surface temperature and facilitate dry heat flux in warm or cool environments, niacin ingestion has the potential to facilitate heat loss from the body to the environment. In this study, skin blood flow and core temperature were measured before and after niacin ingestion in eight subjects. Each subject was tested on two occasions in climatic conditions of 30°C with moderate humidity. Following niacin ingestion, peak forearm blood flow (FBF) by venous occlusion plethysmography averaged 8.0(1.7) ml/100ml/min from an average baseline of 2.2(0.5) ml/100ml/min, an increase of 265%. Forearm skin blood flow (laser doppler flowmetry, LDF) increased 310% (83) at peak niacin vasodilation to 13.1 (4.1) ml/100ml/min from the baseline of 3.4 (1.4) ml/100ml/min. Chest skin blood flow (LDF) increased 550% (154) compared to baseline. Higher skin blood flow significantly increased heat loss from the skin decreasing core temperature an average of 0.44°C (0.10) after niacin ingestion.

Skin blood flow was also characterized after a seven-minute period of brachial arterial occlusion. Arterial occlusion was done to further characterize the effect(s) of niacin ingestion on skin vasodilation. The occlusion followed abatement of the subjective response to nicotinic acid. That is, occlusion was done when the subject reported lessened surface blood flow or related responses due to niacin ingestion. This subjective reaction was confirmed by skin blood flow responses returning toward baseline. Reactive hyperemia measured by laser doppler flowmetry in forearm skin upon the release of brachial arterial occlusion averaged 11.9 (1.7) ml/100ml/min, an increase of 250(110)% above control blood flow. This hyperemic response was 12% less than peak skin blood flow observed during the maximal niacin effect. Chest skin blood flow was unaffected by the period of arterial occlusion of the brachial artery.

The oral vasodilatory agent, nicotinic acid, increased skin blood flow, increased skin temperature and decreased core temperature as we reported previously. Although widespread skin vasodilation occurred in most subjects, the extent of the vasodilation and the intensity of subjective symptoms varied within and between individuals. Nicotinic acid or niacin ingestion (as a systemic treatment), did not increase skin blood
flow in a reproducible manner between the individuals tested or even within the same individual during repeated testing. In fact, dry heat loss was significantly enhanced by increasing skin blood flow in 63% of experiments. For this reason, the usefulness of oral niacin as a method to increase dry heat loss in a controlled manner is questioned.
INTRODUCTION

Scientific Background

In previous studies from this laboratory, nicotinic acid (niacin) was administered orally to study the control of cutaneous vasodilation in humans (Stephenson, Kolka, 1995; Stephenson, Kolka, 1989). In those studies, skin blood flow increased by 600% compared to control experiments in resting subjects. During exercise, skin blood was 30% higher after nicotinic acid ingestion compared to control exercise conditions. In another study, oral nicotinic acid attenuated the core temperature increase by 0.3°C during moderate exercise in healthy adults clothed in chemical protective clothing (Stephenson, Kolka, 1995). Taken together those experiments suggested increased skin blood flow by pharmaceutical means effectively increased sensible heat flux in exercising humans by widespread cutaneous vasodilation.

A pharmaceutical stimulus to increase skin blood flow is more effective if its site of action is on the vasodilator side of sympathetic blood flow control rather than the vasoconstrictor side of sympathetic skin blood flow control. Activation of cutaneous vasodilation increases skin blood flow by 10-15 ml/100ml/min and maximal dilation of the skin vascular beds following local heating can increase skin blood flow as high as 25 ml/100ml/min (Johnson et al., 1986). In contrast, blocking vasoconstrictor activity increases skin blood flow by 2-3 ml/100ml/min (Johnson et al., 1986). Nicotinic acid (niacin) exhibits vasodilatory effects on the skin vasculature that exceed that observed by a release of vasoconstriction (Kajiser et al., 1979; Stephenson, Kolka, 1995; Stephenson, Kolka, 1989).

Purpose

This study was part of a larger study. In that study, differences in skin blood flow responses at rest and during exercise were characterized between smokers, individuals with high serum cholesterol and individuals with low serum cholesterol. A different effect during exercise was expected from individuals hypothesized to have less
compliant vessels (smokers and hypercholesterolemia). Some individuals within each group (smokers, high cholesterol or low cholesterol) chose not to participate in the niacin study, so a comparison among all three groups could not be done with the data collected in this substudy. The data in this report are unique to the subset of volunteers who chose to participate (subjects A,B,C,D,E,F,G and H). This sub-study was done to determine whether the ingestion of the systemic vasodilatory drug (nicotinic acid, niacin) would have predictable and reproducible physiological responses, specifically for including chest and forearm skin blood flow response, in a group of healthy adult volunteers. Additionally, skin blood flow was characterized during reactive hyperemia following brachial artery occlusion following niacin ingestion to examine if the hyperemic response would exceed the niacin induced cutaneous vasodilatory response.

Military Relevance

The U.S. Army Medical and Materiel Command's Science and Technology Objective III. T. "Prevention of Heat Injuries" defines a task (TB) including research demonstrating the efficacy of regional cooling strategies via manipulation of current microclimate cooling techniques. In these experiments, nicotinic acid, a systemic vasodilatory compound, was used to dilate cutaneous vasculature in humans to enhance heat loss measured at the forearm.

A logistical problem facing soldiers training or working in hot environments, or in soldiers wearing chemical protective clothing, is heat stress. Microclimate cooling systems (MCC) are worn, generally under clothing, to reduce heat stress in those situations (Pandolf, 1995). Unfortunately, the cooling capacity of MCC is limited by power supplied to cool the specific liquid or air used with the system.

Pharmacologic and physiologic strategies affecting regional skin blood flow in humans might optimize cooling with the power available. One pharmacologic approach that could be used is treatment with a vasodilatory compound to increase cutaneous vasodilation under the MCC. By enhancing cutaneous vasodilation, sensible heat flux from the skin under the MCC can be enhanced. A difficulty currently observed with
MCC systems is the temperature of the air or liquid medium may actually cause blood vessels of the underlying skin to constrict in response to cooling. If either this local cooling of the cutaneous vasculature was blocked by slightly increasing the temperature of the cooling medium, or if the vasodilatory reflex was activated by an exogenous vasodilator, the possibility for enhanced sensible heat flux at specific regional skin sites exists. This adds the possibility for additional benefit that power supplied to the MCC could be reduced.

**METHODS**

Eight volunteers (2 females, 6 males) were informed of all test procedures before inclusion. All subjects were briefed on the purpose, procedures, and potential hazards of this protocol. Investigators adhered to guidelines established for research on humans in USARIEM M 70-68, AR 70-25 and USAMRMC 70-25 Use of Volunteers in Research. The individual characteristics of the eight subjects are given in Table 1. The average (mean (SD)) age was 31.5 (11.9) years, height 1.75 (0.11) m, mass 75.3 (14.3) kg, serum cholesterol 160 (52) mg/dl and the total cholesterol to high density lipoprotein cholesterol (HDL) was 3.6 (0.6). Females did not use oral contraceptive drugs in the previous six months and were studied during days 2-6 of their menstrual cycle.

**Preliminary Testing.** Prior to any experimental testing the Medical Monitor cleared all volunteers for participation. Clearance included a fasting lipid profile (triglycerides, high-density lipoprotein (HDL) and total cholesterol measurements. Chronic use of aspirin, ibuprofen or any other medication affecting endothelial or smooth muscle function disqualified volunteers. In addition, a challenge dose of nicotinic acid (100 mg) was administered to the test subject under medical supervision before any experiments were done. This challenge reduced the risk of an idiosyncratic response to niacin ingestion in an individual.

Subjects B and D were in the high cholesterol group, subjects F and H were
smokers, subjects A,C,E and G were in the low cholesterol group and within that group subject G had very low total cholesterol (Table 1). There was no attempt to statistically compare the physiological responses following niacin treatment between the three groups in this sub study.

**Environmental Conditions** The study was run in a climatic chamber at the U.S. Army Research Institute for Environmental Medicine. The ambient dry bulb temperature was 30°C (86°F) and the ambient dew-point temperature was 12°C (54°F).

### Table 1. Subject Profiles

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Ht (m)</th>
<th>Mass (kg)</th>
<th>Cholesterol</th>
<th>HDL Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>M</td>
<td>19</td>
<td>1.93</td>
<td>103.5</td>
<td>149</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>19</td>
<td>1.69</td>
<td>61.3</td>
<td>206</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>43</td>
<td>1.76</td>
<td>78.5</td>
<td>141</td>
</tr>
<tr>
<td>D</td>
<td>F</td>
<td>46</td>
<td>1.58</td>
<td>61.4</td>
<td>252</td>
</tr>
<tr>
<td>E</td>
<td>F</td>
<td>43</td>
<td>1.73</td>
<td>70.3</td>
<td>145</td>
</tr>
<tr>
<td>F</td>
<td>M</td>
<td>32</td>
<td>1.70</td>
<td>74.0</td>
<td>127</td>
</tr>
<tr>
<td>G</td>
<td>M</td>
<td>21</td>
<td>1.85</td>
<td>78.5</td>
<td>100</td>
</tr>
<tr>
<td>H</td>
<td>M</td>
<td>18</td>
<td>1.75</td>
<td>72.3</td>
<td>164</td>
</tr>
</tbody>
</table>

**Vasodilatory Stimuli.** Two stimuli were used to elicit increased skin blood flow in this study. Oral niacin treatment (300-400 mg; 5 mg/kg) was used to stimulate cutaneous vasodilation on the forearm, as measured by venous occlusion plethysmography (Doherty et al. 1993; Whitney, 1953; Hokanson et al. 1975) and laser Doppler flowmetry. In addition, cutaneous dilation on the chest was measured by laser Doppler flowmetry. Post-occlusive (brachial artery) reactive hyperemia was used to measure vasodilation of cutaneous vessels in the forearm near the end of each niacin ingestion experiment.

**Test Procedures.** The subjects fasted overnight, and refrained from drinking alcohol 24
prior to the experiment. Water ingestion was permitted upon awakening. Smokers refrained from smoking upon awakening and prior to the experiments. Before the experiment, a 5 ml venous blood sample was drawn for determination of triglycerides, total cholesterol and HDL cholesterol to confirm the lipid profile for each subject. The time of the experiment was at approximately the same time of day for each subject to control for circadian differences in skin blood flow (SkBF) and thermoregulation (Stephenson et al. 1984; Wenger et al. 1976). Each subject did the experiment on two separate days separated by at least 3 days.

The subjects arrived at the environmental test chamber dressed in shorts, singlet, and shoes and socks. Electrocardiographic electrodes and leads were attached to the torso for the measurement of heart rate. Each individual was weighed and sat in a comfortable chair. (S)he swallowed a thermistor or thermocouple encapsulated in water-proof insulation for the measurement of esophageal temperature ($T_{es}$). The esophageal thermocouple was inserted to a depth of about 25% of the individual's height. Thermocouples (copper-constantan) were attached to the skin at eight sites. Venous occlusion plethysmography was used to measure forearm blood flow (FBF) (Doherty et al. 1993; Whitney, 1953; Hokanson et al. 1975), laser Doppler velocimetry was used to measure skin blood flow (SkBF) (Johnson et al. 1984) on the forearm and chest. Local skin sweating rate was measured on the chest and forearm in a contralateral position to the laser Doppler probe. An automatic blood pressure monitor (Accutorr) was used to determine systolic and diastolic blood pressure.

After all instruments were attached to the subject, a twenty-minute control period began. During this period, esophageal and skin temperatures, forearm blood flow, skin blood flow, and local sweating rate were measured every 0.5 min, and blood pressure and heart rate were measured every 5 min. After this control period, the volunteer ingested 300-400 mg niacin, depending on body weight. The target dose was 5 mg niacin per kg body weight. After niacin ingestion, all data were collected each 0.5 min. Once the subjective response to niacin vasodilation (and the reversal of the dilation
based on laboratory measurements occurred, post-occlusive hyperemia (brachial artery occlusion) was measured on the forearm. The blood pressure cuff was inflated to 200 Torr to occlude brachial arterial blood flow. This cuff remained inflated for 7 min. The occlusion was released and the pattern and magnitude of the hyperemic response was measured for an additional 5 min. If the niacin-induced vasodilation persisted, data were collected until the vasodilation diminished and then the arterial occlusion was done.

STATISTICAL ANALYSIS

Descriptive statistics for the physiological responses following niacin ingestion are presented throughout the text. Comparisons of core temperature, skin temperature, skin blood flow, heart rate and blood pressure between control periods, niacin vasodilation and reactive hyperemia were done by analysis of variance or paired t-tests procedures whenever appropriate.

RESULTS and DISCUSSION

The data for all sixteen experiments for all eight subjects are shown in Figures 1 through 16. The responses of the individual subjects differed slightly from each other, although in general, the characteristic responses previously observed following niacin ingestion were apparent (Stephenson, Kolka, 1995; Stephenson, Kolka, 1989). These physiological responses are presented in Table 2.
Table 2. Physiological Summary

<table>
<thead>
<tr>
<th></th>
<th>Onset time</th>
<th>Dilation Duration</th>
<th>Forearm blood flow increase</th>
<th>Skin blood flow increase</th>
<th>Temperature decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp 1</td>
<td>13.1 min</td>
<td>65 min</td>
<td>5.8 ml</td>
<td>322%</td>
<td>0.49°C</td>
</tr>
<tr>
<td></td>
<td>(2.7)</td>
<td>(3)</td>
<td>(1.3)</td>
<td>(72)</td>
<td>(0.09)</td>
</tr>
<tr>
<td>Exp 2</td>
<td>17.6 min</td>
<td>70 min</td>
<td>5.9 ml</td>
<td>316%</td>
<td>0.38°C</td>
</tr>
<tr>
<td></td>
<td>(2.7)</td>
<td>(9)</td>
<td>(2.0)</td>
<td>(97)</td>
<td>(0.08)</td>
</tr>
</tbody>
</table>

The data in Table 2 represent all experiments and are divided into the mean data collected in the first and the second experiments from all subjects. There were no significant differences in onset time, duration of the niacin-induced dilation, the magnitude of the forearm blood flow or skin blood flow increase after niacin ingestion or the magnitude of the decrease in core temperature between the repeated experiments on any subject. That said, there was significant variability of the responses of the individual subjects and from an individual from each of the two experiments. For example, the range of onset time for vasodilation was 7-26 minutes for the first trial and 8-28 minutes for the second trial. The decrease in core temperature ranged from 0.18-0.85°C in the first trial and 0.19-0.84°C in the second trial.

The data in Figures 1 through 16 show the individual responses of the subjects during twenty minutes of control data collection, niacin ingestion and reactive hyperemic response following brachial artery occlusion. The nine panels in each figure show core and mean skin temperatures, local sweating rate, forearm and skin blood flows, systolic and diastolic blood pressure and heart rate. Niacin ingestion is noted by the rapid decrease in esophageal temperature at the twenty-minute mark. The average time (all experiments) for a significant change in skin blood flow (forearm and chest blood flow)
after niacin ingestion was 15.4 (2.8) minutes. Mean skin temperature increased as a result of the larger proportion of blood circulating through the skin vascular beds. Esophageal temperature decreased following increased sensible or dry heat flux from the skin surface (temperature at 34-35°C) to the ambient air (30°C). The average decrease in esophageal temperature after niacin ingestion was 0.44 (0.10)°C. This followed an absolute increase in FBF of 5.8 (1.7) ml/100ml/min from a baseline control of 2.2 (0.5) ml/100ml/min and a relative change in forearm and chest blood flow of 310 (83) and 550(154)%, respectively. The absolute change in skin blood flow (LDF) on the forearm was 9.7 (1.7) ml/100ml/min. The duration of cutaneous vasodilation averaged 67.2 (3.2) minutes before a significant reversal of the dilation occurred. Widespread cutaneous vasodilation transiently decreased diastolic blood pressure with concomitant increases in heart rate. The observed changes in arterial pressure are clearly seen in subjects D and E and to a lesser extent in some of the other subjects.

The hyperemic response is observed in all figures at approximately ninety minutes. This is shown in the forearm laser Doppler data shown in the middle panel of each figure. This manipulation was done after a change in direction of skin and core temperature toward control. In all experiments occlusion was complete and lasted from five to seven minutes. Mean data for the hyperemic procedure are shown in Figure 15. Skin blood flow on the forearm (LDF) increased an average 8.5(1.8) ml/100ml/min after the release of arterial occlusion. The peak blood flow observed during hyperemia following the release of arterial occlusion was less than the skin blood flow seen during the peak niacin induced skin vasodilation (9.7(1.7)ml/100ml/min; p<0.05).

The mean forearm skin blood flow response following oral niacin treatment is shown in Figure 18. The dose of niacin ingested by the subjects in these experiments resulted in similar responses, but of a lower magnitude than we had previously reported (Stephenson, Kolka, 1995; Stephenson, Kolka, 1989). One difficulty with oral ingestion of nicotinic acid, is the observation of variable responses between and among individuals. Every attempt was made to account for, or control, as many variables, i.e
over-the-counter medications, diet, caffeine ingestion, sleep, exercise level, etc., and still the vasodilatory response to oral niacin ingestion was highly variable. It was clear that subjects experiencing the largest cutaneous vasodilation (measured by venous occlusion plethysmography) at the forearm, had the largest decrease in core temperature.

Skin blood flow responses following brachial artery occlusion provided an additional avenue to examine the magnitude of increased skin blood flow after niacin ingestion. It was expected that hyperemia following brachial artery inclusion would significantly increase blood flow. In these experiments, the skin blood flow response after arterial occlusion did increase skin blood flow as expected. Reactive hyperemia following arterial occlusion is not limited to the surface vessels of the skin, although only skin blood flow was measured. The increased skin blood flow was less than observed at the peak effect following oral niacin treatment. It is known that nicotinic acid dilates surface vessels via a prostaglandin-linked mechanism (Kaiser et al., 1979). It is also known that nitric oxide is involved in dilation of blood vessels (Selwyn and Braunwald, 1991). The dilation caused by nicotinic acid ingestion may have resulted in near maximal skin blood flow for the conditions of this study, or that the sustained dilation of surface vessels after niacin ingestion “exhausted” or depleted a dilatory substance or cofactor such that further dilation was inhibited or prevented.

The purpose of this study was to further our knowledge of nicotinic acid induced vasodilation of the skin vascular beds. However, the present results showed more variable responses than our previous studies (Stephenson, Kolka, 1995; Stephenson, Kolka, 1989). Combined with its undesirable effects on systemic blood pressure in some individuals (Stephenson and Kolka, 1995), niacin ingestion to facilitate increased sensible heat loss has limited application. For example, the average increase forearm skin blood flow was half that observed previously (Stephenson, Kolka, 1989). Some subjects showed little decrease in core temperature after niacin ingestion and in others skin vasodilation occurred in one experiment and not in the other experiment. There
was considerable variability and no consistent, reproducible response from all subjects in these experiments. Yet, significant enhancement of dry heat loss was observed in most (63%) experiments.
F1

Suspect that Dew Point sensor was not ventilated 0-22 min.
CONCLUSIONS

This study was done to determine whether the ingestion of nicotinic acid would have predictable and reproducible physiological responses on chest and forearm skin blood flow. In addition, skin blood flow was measured after brachial artery occlusion to see if the hyperemic response exceeded niacin-induced cutaneous vasodilation. Oral niacin treatment did dilate skin vessels. However, the magnitude of the vasodilation was not reproducible between subjects or within an individual subject. We attempted to pharmacologically induce cutaneous vasodilation of the skin vasculature in skin regions that are normally covered by Microclimate Cooling systems (MCC), and systematically increase surface skin temperature to theoretically increase or improve the temperature gradient between the skin surface and the MCC. If skin blood flow was predictably altered, increased sensible heat flux through the skin could be predicted. This possibility has implications for improving the efficacy and efficiency of microclimate cooling systems. In our hands, whole body vasodilation caused by niacin ingestion may not be a feasible intervention to predictably improve sensible heat flux from soldiers dressed in chemical protective garments, because the degree of cutaneous vasodilation was not predictable between subjects. Even more discouraging is the observation that the magnitude of niacin-induced vasodilation was not predictable within a subject.
REFERENCES


