Repeated Thermal Therapy Improves Impaired Vascular Endothelial Function in Patients With Coronary Risk Factors

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**OBJECTIVES**
We sought to determine whether sauna therapy, a thermal vasodilation therapy, improves endothelial function in patients with coronary risk factors such as hypercholesterolemia, hypertension, diabetes mellitus and smoking.

**BACKGROUND**
Exposure to heat is widely used as a traditional therapy in many different cultures. We have recently found that repeated sauna therapy improves endothelial and cardiac function in patients with chronic heart failure.

**METHODS**
Twenty-five men with at least one coronary risk factor (risk group: 38 ± 7 years) and 10 healthy men without coronary risk factors (control group: 35 ± 8 years) were enrolled. Patients in the risk group were treated with a 60°C far infrared-ray dry sauna bath for 15 min and then kept in a bed covered with blankets for 30 min once a day for two weeks. To assess endothelial function, brachial artery diameter was measured at rest, during reactive hyperemia (flow-mediated endothelium-dependent dilation [%FMD]), again at rest and after sublingual nitroglycerin administration (endothelium-independent vasodilation [%NTG]) using high-resolution ultrasound.

**RESULTS**
The %FMD was significantly impaired in the risk group compared with the control group (4.0 ± 1.1% vs. 8.2 ± 2.7%, p < 0.0001), while %NTG was similar (18.7 ± 4.2% vs. 20.4 ± 5.1%). Two weeks of sauna therapy significantly improved %FMD in the risk group (4.0 ± 1.7% to 5.8 ± 1.3%, p = 0.001). In contrast, %NTG did not change after two weeks of sauna therapy (18.7 ± 4.2% to 18.1 ± 4.1%).

**CONCLUSIONS**
Repeated sauna treatment improves impaired vascular endothelial function in the setting of coronary risk factors, suggesting a therapeutic role for sauna treatment in patients with risk factors for atherosclerosis. (J Am Coll Cardiol 2001;38:1083–8) © 2001 by the American College of Cardiology
mean age: 38 ± 7 years, range: 25 to 51 years) and 10 healthy men without coronary risk factors (control group, mean age: 35 ± 8 years, range: 21 to 47 years). None of the patients had coronary artery disease or was taking medications. Written informed consent was obtained from all of the individuals, and the protocol was approved by the Ethics Committee of the Faculty of Medicine, Kagoshima University.

**Laboratory examination.** Fasting blood was obtained in the morning before and after two weeks of sauna therapy for the measurement of biochemical parameters. Plasma concentrations of thiobarbituric acid reactive substances (TBARS) were measured using the thiobarbituric acid reaction method.

**Definition of conventional coronary risk factors.** Hypertension was defined as a supine systolic blood pressure (BP) ≥140 mm Hg or a diastolic BP ≥90 mm Hg measured by a mercury sphygmomanometer after 15 min of rest on two separate occasions. Hypercholesterolemia was defined as a fasting blood total cholesterol ≥220 mg/dl. Diabetes mellitus was defined as a fasting plasma glucose concentration ≥126 mg/dl. Obesity was defined as a body mass index ≥26.4. Smokers were defined as individuals who smoked ≥20 cigarettes per day at the time of the study.

**Sauna therapy.** A far infrared-ray dry sauna system (Olympia Co., Miyazaki, Japan) was used for sauna therapy. Patients underwent sauna therapy at 60°C for 15 min and then were kept supine in a bed outside the sauna for 30 min with sufficient warmth provided by blankets (32). Sauna therapy was performed in the risk group once a day for two weeks. The patients maintained their other daily habits.

**Vascular function.** To assess vascular function, we used a noninvasive technique described by Celermajer et al. (35). Briefly, a high-resolution Doppler ultrasound system (HDI-5000; ATL, Bothel, Washington) equipped with a 12-MHz linear-array transducer was used to measure the diameter and flow velocity of the left brachial artery. Individuals rested in a supine position for 15 min before the first scan and were kept supine throughout the study. The left brachial artery was scanned in both long- and short-axis views to obtain the maximum dimension. We confirmed the center of the artery when the clearest images of the anterior and posterior walls of the artery were obtained, as described previously (1). After the confirmation, we scanned in longitudinal section throughout the study. The first resting image was recorded, and arterial flow velocity was measured using a pulsed Doppler signal directed 60° to the longitudinal axis of the artery. After measuring the BP of the right upper limb, a cuff was inflated around the left forearm to a pressure of 20 mm Hg above the systolic BP for 5 min. During inflation, we confirmed that no blood flow was present downstream of the cuff with photoplethysmography monitoring (FCP-4731, IB-70, Fukuda Denshi, Kumamoto, Japan) of the second finger of the left hand. The second scan was recorded continuously for 30 s before and 3 min after rapid cuff deflation. Fifteen minutes later, a repeat resting scan was performed. Sublingual nitroglycerin (NTG) spray (300 µg; Myocol Spray, Toa Eiyo Co., Tokyo, Japan) was then administered, and the last scan was recorded 3 to 5 min later. All images were recorded on S-VHS videotape using an MD830 videocassette recorder (SONY, Tokyo, Japan).

The arterial diameter was measured between the intima-blood interfaces on the anterior and posterior walls with ultrasonic calipers (Fig. 1) during the onset of the R-wave of the electrocardiogram for five consecutive cardiac cycles, and the five measurements were then averaged. These measurements were performed by two blinded observers. Percent flow-mediated dilation (%FMD) is expressed as the maximum percent change in diameter 45 to 60 s after rapid cuff release normalized to the first resting scan (endothelium-dependent vasodilation). The maximum dilation after NTG administration is also expressed as the percent change normalized to the repeat resting scan ([%NTG] endothelium-independent vasodilation). Blood flow was calculated by multiplying the velocity-time integral of the Doppler flow signal by the heart rate and cross-sectional area of the brachial artery. Reactive hyperemia is defined as the maximum flow during the first 15 s after cuff release divided by the baseline flow. Vascular function was evaluated once in the control group and twice in the risk group (before the first sauna treatment and the day after the last sauna treatment).

Interobserver variability was determined by calculating the mean and standard deviation for the difference in the measurements made by the two observers for 20 arterial studies. The interobserver variability for %FMD was 0.2 ± 1.1%.

**Abbreviations and Acronyms**

- BP = blood pressure
- eNOS = endothelial isoform of nitric oxide synthase
- NO = nitric oxide
- NTG = nitroglycerin
- TBARS = thiobarbituric acid reactive substances
- %FMD = percent flow-mediated dilation
- %NTG = percent nitroglycerin-induced dilation

**Figure 1.** Representative example of ultrasound images of brachial artery at rest (left) and 60 s after cuff release (right). The diameter of the artery increased from 3.22 mm (rest) to 3.48 mm (after cuff release) in response to increased blood flow. In this case, the percentage of flow-mediated dilation was 8.1%.
In preliminary studies in eight patients with coronary risk factors, we confirmed that the %FMD did not change at a two-week interval without any modification of coronary risk factors (4.6 ± 2.5% vs. 4.7 ± 1.8%, \( p = \text{NS} \)). After this confirmation, we started this study.

**Statistical analysis.** Measurements are expressed as the mean ± SD. A two-sided paired Student \( t \) test was used to compare changes in vascular responses and laboratory values before and after sauna therapy. A value of \( p < 0.05 \) was considered statistically significant.

**RESULTS**

**Clinical characteristics.** The clinical characteristics of both groups are summarized in Table 1. In the risk group, 8 patients had hypertension; 3 patients had diabetes mellitus; 8 patients had hypercholesterolemia, and 15 patients were current smokers (Table 1).

**Effects of sauna therapy on body weight, heart rate and BP.** The body weight decreased significantly (75.2 ± 9.9 kg to 74.9 ± 9.9 kg, \( p < 0.05 \)), while the heart rate did not change (68 ± 10 beats/min to 68 ± 10 beats/min, \( p = \text{NS} \)) after two weeks of sauna therapy. Both systolic and diastolic BP decreased significantly (systolic BP: 128 ± 18 mm Hg to 124 ± 17 mm Hg, \( p < 0.01 \); diastolic BP: 77 ± 17 mm Hg to 72 ± 16 mm Hg, \( p < 0.05 \)) after two weeks of sauna therapy (Table 2).

**Effects of sauna therapy on biochemical parameters.** After two weeks of sauna therapy, liver and renal function did not change. The hematocrit and serum total cholesterol, triglyceride, high-density lipoprotein cholesterol and uric acid concentrations did not change significantly. In contrast, the fasting plasma glucose concentration decreased significantly (99 ± 25 mg/dl to 94 ± 16 mg/dl, \( p < 0.05 \)). The plasma TBARS concentration did not change (2.8 ± 0.6

### Table 1. Clinical Characteristics of the Control and Risk Groups

<table>
<thead>
<tr>
<th></th>
<th>Control Group (( n = 10 ))</th>
<th>Risk Group (( n = 25 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>35 ± 8</td>
<td>38 ± 7</td>
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</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>0/10</td>
<td>8/25 (32)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>187 ± 12</td>
<td>214 ± 44</td>
<td>0.07</td>
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<tr>
<td>Hypertension (%)</td>
<td>0/10</td>
<td>8/25 (32)</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>122 ± 11</td>
<td>128 ± 18</td>
<td>0.34</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>76 ± 8</td>
<td>77 ± 17</td>
<td>0.90</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>0/10</td>
<td>3/25 (12)</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>91 ± 7</td>
<td>99 ± 25</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>0/10</td>
<td>15/25 (60)</td>
<td></td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>0/10</td>
<td>9/25 (36)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.2 ± 1.8</td>
<td>25.6 ± 2.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Resting arterial diameter (mm)</td>
<td>3.6 ± 0.4</td>
<td>3.9 ± 0.3</td>
<td>0.09</td>
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<tr>
<td>%FMD (%)</td>
<td>8.2 ± 2.7</td>
<td>4.0 ± 1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%NTG (%)</td>
<td>20.4 ± 5.1</td>
<td>18.7 ± 4.2</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Values are expressed as the mean ± SD.

**BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; %FMD = percentage of flow-mediated dilation; %NTG = percentage of nitroglycerin-induced dilation.**

### Table 2. Changes in Clinical Parameters After Two Weeks of Sauna Treatment

<table>
<thead>
<tr>
<th></th>
<th>Before Sauna</th>
<th>After Two Weeks of Sauna</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>75.2 ± 9.9</td>
<td>74.9 ± 9.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 10</td>
<td>68 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128 ± 18</td>
<td>124 ± 17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77 ± 17</td>
<td>72 ± 16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>47.6 ± 2.9</td>
<td>47.2 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>214 ± 44</td>
<td>208 ± 34</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/ml)</td>
<td>268 ± 327</td>
<td>221 ± 159</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>51 ± 11</td>
<td>50 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>6.8 ± 1.8</td>
<td>6.6 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>99 ± 25</td>
<td>94 ± 16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TBARS (nmo/l)</td>
<td>2.8 ± 0.6</td>
<td>2.9 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Resting arterial diameter (mm)</td>
<td>3.9 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Reactive hyperemia (%)</td>
<td>398 ± 170</td>
<td>352 ± 215</td>
<td>NS</td>
</tr>
<tr>
<td>%FMD (%)</td>
<td>4.0 ± 1.7</td>
<td>5.8 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%NTG (%)</td>
<td>18.7 ± 4.2</td>
<td>18.1 ± 4.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as the mean ± SD.

HDL cholesterol = high-density lipoprotein cholesterol; TBARS = thiobarbituric acid reactive substances; %FMD = percentage of flow-mediated dilation; %NTG = percentage of nitroglycerin-induced dilation.
Effects of sauna therapy on vascular function. No patient had any significant arterial stenosis or plaques in the brachial artery studied. In the control group, the mean resting arterial diameter was 3.6 ± 0.4 mm, and the %FMD (endothelium-dependent vasodilation) and the %NTG (endothelium-independent vasodilation) were 8.2 ± 2.7% and 20.4 ± 5.1%, respectively. In the risk group, the mean resting arterial diameter was larger, but not significantly larger than that in the control group (3.9 ± 0.3 mm vs. 3.6 ± 0.4 mm, p = NS). The %FMD was significantly lower than that in the control group (4.0 ± 1.7% vs. 8.2 ± 2.7%, p < 0.0001), but the %NTG was not different from that in the control group (18.7 ± 4.2% vs. 20.4 ± 5.1%, p = NS) (Table 1). After two weeks of sauna therapy, the mean resting arterial diameter in the risk group did not change significantly (3.9 ± 0.3 mm to 3.9 ± 0.3 mm, p = NS). In addition, reactive hyperemia also did not change (398 ± 170% to 352 ± 215%, p = NS). While the %FMD increased significantly from the baseline value (4.0 ± 1.7% to 5.8 ± 1.3%, p < 0.001; Table 2, Fig. 2), the %NTG did not change (18.7 ± 4.2% to 18.1 ± 4.1%, p = NS) after two weeks of sauna therapy (Table 2).

Effects of a single sauna therapy on blood flow of the brachial artery. To assess the degree of blood flow increase of the brachial artery after a single sauna therapy, we measured blood flow at rest and during sauna therapy in eight patients with coronary risk factors. Blood flow of the brachial artery significantly increased by 68% after 15 min of sauna therapy and remained elevated by 51% 30 min after sauna therapy. %p < 0.0001 vs. before sauna therapy; **p < 0.05 vs. before sauna therapy.

DISCUSSION
In this study we found that two weeks of sauna treatment improves impaired endothelial function in patients with conventional coronary risk factors, whereas the vascular response to NTG does not change. This suggests that long-term thermal therapy may play a preventive role in atherosclerosis.

Possible mechanisms of endothelial dysfunction by coronary risk factors. In the endothelium, the amino acid L-arginine is converted to L-citrulline and NO by the endothelial isoform (eNOS) of NO synthase. Nitric oxide is an important vasodilator substance and helps prevent atherosclerosis by maintaining vasodilation and inhibiting platelet aggregation, leukocyte adhesion and proliferation of smooth muscle cells in the arterial wall (36). Therefore, NO plays an important role in endothelial function. We could not determine the precise mechanism by which repeated sauna treatment improves impaired endothelial function in patients with conventional coronary risk factors. However, three major mechanisms responsible for endothelial dysfunction induced by these risk factors have been proposed. First, an alteration in the signaling pathway that activates eNOS has been observed in the hypercholesterolemic condition (37,38). Second, reduced expression of eNOS: reduced eNOS gene and protein expression have been reported in cultured endothelial cells exposed to cigarette smoke extract (39) and in endothelial cells from spontaneously hypertensive rats (40). Endothelial isoform of nitric oxide synthase protein expression is also reduced in skeletal muscle from streptozotocin-induced diabetic rats (41). Third, reduced bioavailability of NO because of oxidative stress: because free radicals can inactivate NO (42), oxidative stress reduces the bioavailability of NO (43–48). More-
Repeated Sauna Improves Endothelial Function

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Repeated sauna therapy improves impaired endothelial function in patients with coronary risk factors, suggesting a preventive role for thermal therapy for atherosclerosis.

Study limitations. Because we evaluated the effects of sauna treatment on endothelial function in a small number of individuals with coronary risk factors, the importance of each risk factor remains uncertain. Further studies in larger numbers of individuals with conventional coronary risk factors are needed.

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