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 ($4.0 \pm 1.7\%$ vs. $8.2 \pm 2.7\%$, $p < 0.0001$), while %NTG was similar ($18.7 \pm 4.2\%$ vs. $20.4 \pm 5.1\%$). Two weeks of sauna therapy significantly improved %FMD in the risk group ($4.0 \pm 1.7\%$ to $5.8 \pm 1.3\%$, $p < 0.001$). In contrast, %NTG did not change after two weeks of sauna therapy ($18.7 \pm 4.2\%$ to $18.1 \pm 4.1\%$).
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

Endothelial dysfunction is observed in patients with conventional coronary risk factors such as hyperlipidemia (1), hypertension (2), diabetes mellitus (3) and cigarette smoking (4–6). Endothelial dysfunction is believed to represent an early stage of atherosclerosis. It has been reported that chronic inhibition of nitric oxide (NO) production accelerates neointima formation and impairs endothelial function in hypercholesterolemic rabbits (7). Endothelial function of the brachial artery has been shown to be related to the intima-media thickness of the carotid artery (8). Furthermore, coronary endothelial dysfunction is associated with increased cardiac events and poor prognosis (9,10). Modification of coronary risk factors through the use of cholesterol-lowering therapy (11–17), antihypertensive therapy (18–21), antioxidant therapy (22–25), L-arginine supplementation (26–29) and estrogen replacement therapy in postmenopausal women (30,31) improves impaired endothelial function in the coronary or brachial arteries.

Exposure to heat is widely used as a traditional therapy in many cultures. However, its precise mechanisms remain unclear. We have previously reported that repeated use of a sauna at 60°C improves hemodynamics and clinical symptoms in patients with chronic heart failure (32,33). In addition, we have recently found that repeated sauna therapy improves endothelial function and decreases plasma brain natriuretic peptide concentrations in patients with chronic heart failure (34).

Therefore, we hypothesized that repeated sauna therapy can improve impaired endothelial function in the setting of conventional coronary risk factors. The purpose of this study was to determine whether repeated sauna therapy improves impaired endothelial function in patients with coronary risk factors.

METHODS

Study population. The study population was comprised of 25 men with at least one coronary risk factor (risk group,

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%.

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
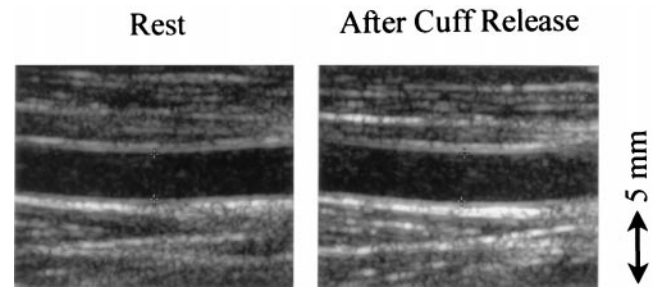
using a pulsed Doppler signal directed 60° to the longitudinal axis of the artery. After measuring the BP of the right upper limb, a cuff was inflated around the left forearm to a pressure of 20 mm Hg above the systolic BP for 5 min. During inflation, we confirmed that no blood flow was present downstream 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%.

Table 1. Clinical Characteristics of the Control and Risk Groups

	Control Group (n = 10)	Risk Group (n = 25)	p Value
Age (yrs)	35 ± 8	38 ± 7	0.25
Hypercholesterolemia (%)	0/10	8/25 (32)	
Total cholesterol (mg/dl)	187 ± 12	214 ± 44	0.07
Hypertension (%)	0/10	8/25 (32)	
SBP (mm Hg)	122 ± 11	128 ± 18	0.34
DBP (mm Hg)	76 ± 8	77 ± 17	0.90
Diabetes mellitus (%)	0/10	3/25 (12)	
Fasting plasma glucose (mg/dl)	91 ± 7	99 ± 25	0.29
Smoking (%)	0/10	15/25 (60)	
Obesity (%)	0/10	9/25 (36)	
BMI	23.2 ± 1.8	25.6 ± 2.8	0.02
Resting arterial diameter (mm)	3.6 ± 0.4	3.9 ± 0.3	0.09
%FMD (%)	8.2 ± 2.7	4.0 ± 1.7	<0.0001
%NTG (%)	20.4 ± 5.1	18.7 ± 4.2	0.32

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.

In preliminary studies in eight patients with coronary risk factors, we confirmed that the %FMD did not change at two-week interval without any modification of coronary risk factors (4.6 ± 2.5% vs. 4.7 ± 1.8%, p = 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 = 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 2. Changes in Clinical Parameters After Two Weeks of Sauna Treatment

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

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.
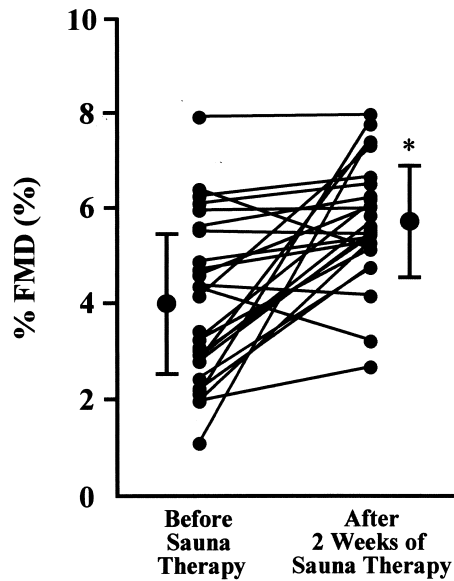
Figure 2. Changes in individual percentage of flow-mediated dilation (%FMD) after two weeks of sauna therapy. *p < 0.001 vs. before sauna therapy.
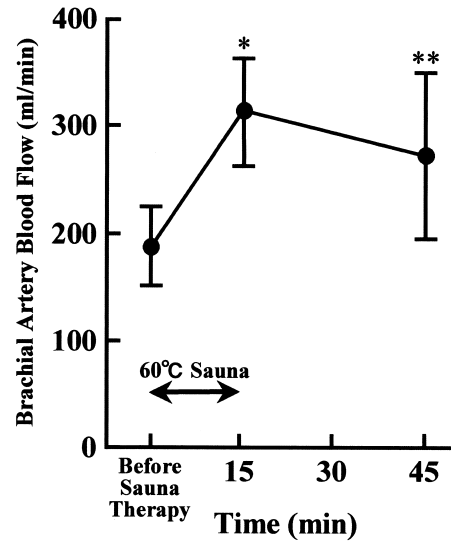

Figure 3. Changes in blood flow of the brachial artery during a single sauna therapy in eight subjects with coronary risk factors. Blood flow significantly increased by 68% after 15 min of sauna therapy and remained elevated by 51% 30 min after sauna therapy. *p < 0.0001 vs. before sauna therapy; **p < 0.05 vs. before sauna therapy.

nmol/ml to 2.9 ± 0.6 nmol/ml, p = NS) after two weeks of sauna therapy (Table 2).

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 (188 ± 36 ml/min to 313 ± 55 ml/min, p < 0.0001) and remained elevated by 51% 30 min after sauna therapy (188 ± 36 ml/min to 275 ± 80 ml/min, p < 0.05) (Fig. 3).

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-

over, it has been reported that increased oxidized low-density lipoprotein concentrations decrease eNOS activity by displacing eNOS from plasmalemmal caveolae (49). We found that the TBARS concentration did not change after two weeks of sauna treatment (Table 2), suggesting that restoration of bioavailability of NO by decreasing oxidative stress is not involved.

Potential role of shear stress in the improvement of endothelial function. Shear stress is an important factor that increases eNOS activity and stimulates eNOS expression (50–53). We have previously reported that a single sauna treatment induces a 1.5-fold increase in cardiac output in patients with chronic heart failure (32). In addition, we observed that blood flow of the brachial artery significantly increased by 68% during sauna therapy (Fig. 3). This increased blood flow increases shear stress. We have recently demonstrated that the gene expression and protein level of eNOS increase significantly in peripheral arteries from the golden hamster after four weeks of repeated sauna therapy (54). Therefore, we believe that repeated sauna therapy improves endothelial function by increasing eNOS activity and upregulating eNOS expression by increasing shear stress. The significant decrease in BP after two weeks of sauna treatment (Table 2) is probably due to improved endothelium-dependent vasodilation.

In an interesting parallel, exercise has also been demonstrated to improve endothelial dysfunction in healthy older men (55), in patients with chronic heart failure (56) and in patients with the polymetabolic syndrome (57). It has been reported that four weeks of cycle training for 30 min three times per week significantly increases the basal release of NO in healthy volunteers, and a 30-min cycling induces a threefold increase in forearm blood flow and a 15% increase in blood viscosity (58). They suggest that elevated shear stress contributes to the increased basal release of NO. These phenomena are similar to those induced by sauna therapy in this study. Sauna therapy has an advantage in that it is applicable to subjects who are unable to exercise.

Effects of sauna therapy on fasting plasma glucose concentration. A significant decrease in fasting plasma glucose concentration after two weeks of sauna treatment (Table 2) was observed, consistent with the previous report using hot-tub therapy (59). Increased blood flow to skeletal muscles is reported to increase glucose uptake (60); however, further studies will be needed to clarify the precise mechanisms of long-term effects of the sauna therapy on plasma glucose metabolism. Although all the subjects were advised to make no changes in their lifestyle in this study, significant reduction in BP and fasting plasma glucose concentration was observed after two weeks of sauna treatment. These changes were significant but modest and within normal limits, so it is not likely that they contributed to the improvement of endothelial function.

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.

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

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