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CLINICAL STUDIES

A STUDY OF THE HEALTH BENEFITS OF FAR INFRARED SAUNA THERAPY

Conducted by the University of Missouri, Kansas City

Becky Edwards, M.D., Heather Kort D.O

Faculty Staff Advisor: Dr. John Foxworth, PharmD Purpose

RESULTS

The far infrared sauna did lower both systolic and diastolic blood pressure. The diastolic blood pressure in the far infrared group was statistically significant with a p value of .001. In the far infrared group the systolic blood pressure decreased from an average of 130.5 before the study to 124 at the completion of the study.

REPEATED THERMAL THERAPY IMPROVES IMPAIRED VASCULAR ENDOTHELIAL FUNCTION IN PATIENTS WITH CORONARY RISK FACTORS

Takasaki, Yutaka Otsuji, Shinichi Minagoe, Yoshifumi Toyama and Chuwa Tei Masakazu Imamura, Sadatoshi Biro, Takashi Kihara, Shiro Yoshifuku, Kunitsugu

CONCLUSION

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

A Study of the Health Benefits of Far Infrared Sauna Therapy
Conducted by the University of Missouri, Kansas City
Becky Edwards, M.D., Heather Kort D.O
Faculty Staff Advisor: Dr. John Foxworth, PharmD
Overview by Sunlight Saunas

Purpose

Evaluate the effects of far infrared sauna therapy on blood pressure. Change in blood pressure will be the primary outcome measure.

Materials and Methods

- Subjects were randomly assigned to receive sauna sessions in either the far infrared sauna or a control sauna that will emit heat, however not far infrared heat. The saunas looked identical. The subjects had a 30-minute sauna session 3 days a week for 6 weeks at Sunlight Saunas Corporate Headquarters in Lenexa, Kansas. Study conducted June and July 2005.

- Subjects: Included generally healthy subjects between the ages of 21-65 years.

- Exclusion criteria were as follows:
  - Anyone on nitrates or prior heart attack or coronary artery disease
  - Pregnancy (urine pregnancy test will be performed on any woman with child-bearing potential)
  - Lupus
  - MS
  - Hemophilia
  - Sickle cell disease
  - Weight > 220 pounds
  - Breast Implants
  - Changes in medication in the last month or during our study
  - Already using saunas

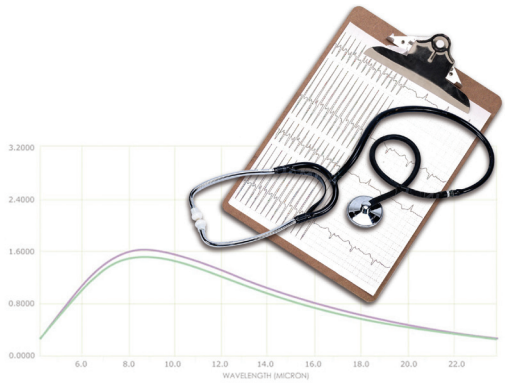
- A power analysis was performed to determine the number of subjects necessary to detect a statistically significant change in the primary outcome measure, mean blood pressure; alpha = 0.05 power=0.80.

- Descriptive statistics were used to summarize study measures. Student's tests were used to compare the groups with regard to mean change in BP, pulse, weight, waist circumference, total cholesterol, LDL and urinary concentrations of mercury.

- At all sauna sessions a registered nurse measured and record the subject's blood pressure, pulse, weight, and waist circumference. The subject rated their pain on a standard pain scale. At the first and last sauna session the nurse drew blood for a fasting lipid profile. Also the subjects will provided a 12-hour urine collection at the first and last visit for analysis of mercury, lead, and cadmium.

Results

- Blood pressure: The far infrared sauna did lower both systolic and diastolic blood pressure. The diastolic blood pressure in the far infrared group was statistically significant with a p value of .001. In the far infrared group the systolic blood pressure decreased from an average of 130.5 before the study to 124 at the completion of the study.



Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 38, No. 4, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01467-X

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 ± 1.7% 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

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,

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Manuscript received January 5, 2001; revised manuscript received May 18, 2001, accepted June 11, 2001.

JACC Vol. 38, No. 4, 2001
October 2001:1083–8

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

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).

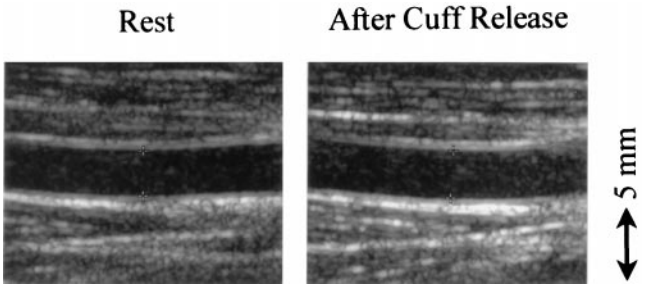

Figure 1. Representative example of ultrasound images of brachial artery at rest **(left)** and 60 s after cuff release **(right)**. The diameter of the artery increased from 3.22 mm (rest) to 3.48 mm (after cuff release) in response to increased blood flow. In this case, the percentage of flow-mediated dilation was 8.1%.

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.

JACC Vol. 38, No. 4, 2001
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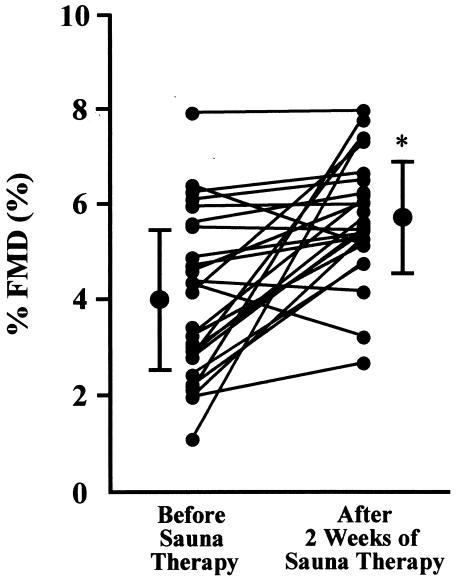

Figure 2. Changes in individual percentage of flow-mediated dilation (%FMD) after two weeks of sauna therapy. *$p < 0.001$ vs. before sauna therapy.

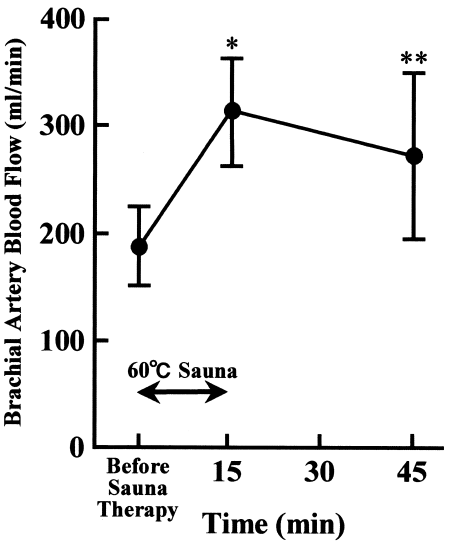

Figure 3. Changes in blood flow of the brachial artery during a single sauna therapy in eight subjects with coronary risk factors. Blood flow significantly increased by 68% after 15 min of sauna therapy and remained elevated by 51% 30 min after sauna therapy. *$p < 0.0001$ vs. before sauna therapy; **$p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

Because of its absence of hydrostatic pressure, thermal therapy with a far infrared-ray dry sauna was performed as previously reported [5]. Patients were placed in a supine position on a bed in a 60°C sauna for 15 min, and once removed, kept on bed rest with a blanket to keep them warm for an additional 30 min. Patients were weighed before and after the sauna treatment; oral hydration with water was used to compensate for lost weight. In contrast, in the nontreated group, subjects were placed in a supine position on a bed in a temperature-controlled (24°C) room for 45 min.

Assessment of clinical symptoms

Clinical symptoms related to dyspnea, fatigue, edema, appetite loss, constipation and insomnia were evaluated by a self-assessment quality-of-life questionnaire. Each item had four grades: remarkably improved, improved, no change or worsened. Patients were classified into three groups based on the results of the questionnaire. Patients who answered "improved" to more than three items were defined as the improved group. Those who answered "worsened" to at least one item were defined as the worsened group. The others were defined as the unchanged group.

Laboratory measurements

A fasting blood sample was obtained in the morning to measure plasma levels of neurohormonal factors, including catecholamines, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), thiobarbituric acid-reactive substances (TBARS) and tumor necrosis factor-alpha (TNF-alpha). Plasma catecholamine (norepinephrine, epinephrine and dopamine) concentrations were measured with high-performance liquid chromatography, and both plasma ANP and BNP concentrations were measured with a radioimmunoassay. Plasma levels of TBARS were measured with the thiobarbituric acid reaction method, and plasma levels of TNF-alpha were measured with an enzyme-linked immunosorbent assay. Chest radiography and echocardiography were also performed. For calculating systemic vascular resistance, stroke volume was measured by two-dimensional and pulsed-wave Doppler echocardiography, monitoring heart rate and blood pressure simultaneously.

Endothelial function

To evaluate endothelial function, we used a previously described noninvasive ultrasound method [29]. Endothelial function was always assessed in a temperature-controlled (24°C) laboratory before dinner. The diameter of the brachial artery was measured on B-mode ultrasound images, using a 12.0-MHz linear-array transducer and high-resolution Doppler ultrasound system (HDI-5000, ATL, Bothel, Washington). The ultrasound images were recorded on a super-VHS videocassette recorder, and the arterial diameter was measured later with ultrasonic calipers by two independent observers who had not participated in the thermal therapy. After measurement of blood pressure of the right arm, a pneumatic tourniquet was placed around the left forearm (at a site distal to the scanned part) and was inflated to a pressure of 20 mm Hg over the systolic blood pressure for 5 min. During inflation, we confirmed with photoplethysmography monitoring (FCP-4731 IB-70, Fukuda Denshi, Kumamoto, Japan) that no blood flow was present downstream of the tourniquet to the second finger of the left hand. Reactive hyperemia was calculated as the maximal flow in the first 15 s after cuff deflation divided by baseline flow. Percent flow-mediated dilation (%FMD) was defined as the percent change in diameter between 60 s after cuff deflation and that on the initial scan. Percent nitroglycerin (%NTG)-induced dilation was also defined as the percent change in diameter between 4 min after administration of sublingual nitroglycerin spray (300 μg) and that on the initial scan. The vessel diameter was measured by two observers who were unaware of the clinical details and the stage of the study. The mean value of the two observations was used. Interobserver variability was determined by calculating the mean ± SD of the difference in the two observers' results from 20 arterial studies. In our laboratory, the interobserver variability for measurement of %FMD was 0.2 ± 1.1%. In a preliminary study, when these procedures were performed at the same time on two different days in eight volunteers, the average intrasubject test-retest difference for the measurements of %FMD was 0.1 ± 0.8%.

Study protocol

Sauna therapy was performed once a day, five days a week and for a total of two weeks in the sauna-treated group. All examinations were performed before the first treatment and on the day after the last treatment.

Statistical analysis

All data are expressed as the mean value ± SD. Data at baseline and after sauna treatment were compared by using the paired *t* test. The relationship between the change in %FMD and the percent improvement in BNP concentration was assessed by Spearman's correlation coefficients. A value of $p < 0.05$ was considered statistically significant.

Results

Clinical findings and laboratory variables

The patients' baseline clinical characteristics are shown in Table 1. All patients enrolled in the study completed the study. None of the sauna-treated patients experienced dyspnea, angina pectoris or palpitations. Clinical symptoms were improved in 17 of 20 patients (improved group) and were unchanged in 3 patients (unchanged group) after the two-week sauna therapy. However, no patient had worsened clinical symptoms. Although the mean heart rate and body weight did not change, systolic blood pressure significantly decreased the day after the two-week sauna treatment ended (Table 1). Furthermore, systemic vascular resistance significantly decreased the day after the two-week sauna treatment ended, as

compared with baseline (2,267 ± 640 dynes·s·cm^{-5} vs. 1,910 ± 451 dynes·s·cm^{-5}, $p < 0.02$). Laboratory variables, including liver function, renal function, electrolytes and hematocrit, did not change after the two-week sauna therapy (data not shown). In contrast, clinical symptoms, hemodynamic data and laboratory variables did not change at the two-week interval in the nontreated group (Table 1).

Table 1. Baseline Clinical Characteristics and Changes in Several Variables at the Two-Week Interval

(<1K)

*Comparison with baseline values. Data are presented as the mean value ± SD.
ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CTR = cardiothoracic ratio; DBP = diastolic blood pressure; %FMD = percent flow-mediated dilation; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; %NTG = percent nitroglycerin; NYHA = New York Heart Association; SBP = systolic blood pressure; TBARS = thiobarbituric acid-reactive substances; TNF-alpha = tumor necrosis factor-alpha.

Vascular function

No patient showed any significant brachial arterial stenosis or plaque. Before sauna and the day after the two-week sauna therapy ended, the vessel diameter of the brachial artery at rest had not changed significantly (3.4 ± 0.6 mm vs. 3.4 ± 0.6 mm), and reactive hyperemia was also unchanged (Table 1). The increase in %FMD during the peak hyperemic response was maximal at 60 s after release of the 5-min arterial occlusion. The increase in %NTG-induced dilation was maximal at 4 min after administration of NTG. In patients with CHF in the nontreated group, %FMD and %NTG-induced dilation did not change at the two week interval (Table 1). Two-week sauna treatment significantly increased %FMD, as compared with that before sauna therapy (4.4 ± 2.5% vs. 5.7 ± 2.5%, P = 0.0006) (Table 1). The data of each patient are shown in Table 2. Percent FMD significantly increased from the baseline value in the improved group (4.5 ± 2.7% vs. 5.9 ± 2.5%, N = 17, $p < 0.01$), but not in the unchanged group (4.2 ± 1.7% vs. 4.0 ± 1.6%, N = 3). Percent NTG-induced dilation was similar before and after the two-week sauna treatment (19.2 ± 6.5% vs. 18.7 ± 6.9%) (Table 1).

Table 2. Characteristics of Each Patient in the Sauna-Treated Group

(<1K)

Abbreviations as in Table 1.

Neurohormonal factors, TBARS and TNF-alpha.

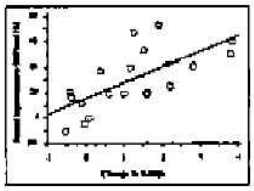
Plasma concentrations of BNP after two weeks of sauna treatment were significantly lower than those at baseline (293 ± 302 pg/ml vs. 441 ± 444 pg/ml, $p < 0.005$) (Table 1). However, ANP and catecholamine concentrations were similar. Plasma levels of TBARS and TNF-alpha did not change after two weeks of sauna therapy. In the nontreated group, these concentrations did not change at the two-week interval.

Variables assessed by chest radiography and echocardiography.

The CTR on chest radiography decreased significantly as compared with that at baseline (Table 1). On echocardiography, the left ventricular end-diastolic dimension (LVEDD) decreased significantly as compared with that at baseline (Table 1). However, there was no difference in the ejection fraction. In contrast, CTR, LVEDD and ejection fraction did not change at the two-week interval in the nontreated group.

Correlation between endothelial and cardiac function

We next examined the correlation between the variables of cardiac function, including ejection fraction, LVEDD, CTR, ANP and BNP, and %FMD of endothelial function in the sauna-treated group. A significant correlation between the change in %FMD and the percent improvement in plasma BNP concentrations was observed ($r = 0.69$, $P = 0.0005$) (Fig. 1).



(5K)

Figure 1. Relationship between the change in percent flow-mediated dilation (%FMD) and the percent improvement in brain natriuretic peptide (BNP) concentration in the sauna-treated group. There is a positive correlation between the change in %FMD and the percent improvement in BNP concentration before and after two weeks of sauna therapy ($r = 0.69$, $P = 0.0005$).

Discussion

The present study indicates that two weeks of sauna therapy improved endothelial function and decreased plasma BNP concentrations in patients with CHF. Furthermore, there is a correlation between the degree of improvement of %FMD and the percent improvement in plasma BNP concentrations. Recent studies have indicated that plasma BNP concentrations are an important marker of cardiac status and prognosis in patients with heart failure [30, 31 and 32]. Therefore, we conclude that repeated 60°C sauna therapy improves peripheral vascular endothelial function, resulting in an improvement in cardiac function in patients with CHF. It should be noted here that body weight and hematocrit did not change with sauna treatment.

Endothelial function and clinical symptoms

We clarified that endothelial function significantly improved after two-week sauna therapy in the brachial artery. We also found that systemic vascular resistance significantly decreased after two-week sauna therapy, suggesting an improvement of endothelial function in resistance vessels. Improved endothelial function leads to dilation of vessels by an increase in NO production. The fact that two weeks of sauna therapy significantly decreased systolic blood pressure (Table 1) in the present study may reflect the improvement in endothelial function. This results in decreased afterload and, thus, increased cardiac output. These changes improve peripheral circulation, which is probably responsible for the improvement in clinical symptoms. Interestingly, in the patients whose clinical symptoms improved, %FMD improved significantly, whereas in the patients whose clinical symptoms did not change, %FMD did not improve.

Possible mechanisms by which sauna therapy improves endothelial and cardiac function

Recent studies have indicated that endothelial function decreases in patients with CHF [9, 10, 11 and 12]. Two major mechanisms for this have been proposed: 1) decreased NO production and 2) increased degradation of NO. The eNOS protein is markedly reduced in the thoracic aorta of dogs with pacing-induced heart failure [33]. Similar results have been reported in rats with heart failure [34]. In addition, Belch et al. [35] reported that plasma lipid peroxides were significantly higher in patients with CHF than in control subjects, suggesting decreased NO bioavailability. In the present study, we could not clarify the precise mechanisms by which long-term sauna therapy improves endothelial function in patients with CHF. However, we have previously demonstrated that thermal therapy increases cardiac output in patients with CHF [5]. This results in increased peripheral blood flow, which increases shear stress in the vessels. In fact, we have recently found that blood flow of the brachial artery significantly increases by 68% after 15 min of sauna therapy and remains elevated by 51% at 30 min after sauna therapy in patients with coronary risk factors [36]. We believe that this increase in shear stress leads to an increase in NO production by the vessels. We have demonstrated that repeated sauna treatment upregulates the eNOS protein in the arterial endothelium, including the aorta and carotid, femoral and coronary arteries, of hamsters [37]. In the present study, we found that there was no difference in plasma levels of TBARS before and after two weeks of sauna therapy (Table 1). Therefore, it is likely that the improvement in endothelial function after long-term, repeated sauna therapy is due to improved NO production by eNOS upregulation in patients with CHF. We believe that eNOS upregulation is due to a prolonged increase in shear stress, but not decreased TNF-alpha levels (Table 1), which is reported to downregulate eNOS expression [38]. Furthermore, eNOS upregulation in the coronary artery may directly improve cardiac function due to an increase in coronary perfusion.

Effects of sauna treatment on natriuretic peptides

In this study, plasma BNP concentrations significantly decreased after two-week sauna therapy, whereas plasma ANP concentrations tended to decrease. We could not clarify the precise mechanisms of this discrepancy. Although both ANP and BNP concentrations are reported to be associated with left ventricular dysfunction, recent studies have revealed that BNP concentrations are more sensitive than ANP concentrations [39 and 40]. Therefore, one explanation may be the shortness of the treatment period.

Clinical implications and study limitations

All patients completed this study, and no patient had worsened clinical symptoms, worsened cardiac arrhythmia, tachycardia, hypotension or dehydration. Furthermore, this sauna therapy may be applicable in patients with CHF who are unable to exercise.

In the present study, we applied sauna therapy to patients with CHF in NYHA functional class II or III and in a stable clinical condition for one month before study entry. Because there were stable patients with CHF, all variables, including BNP concentrations and %FMD, did not change at the two-week interval in the nontreated group. Further studies are needed to investigate the beneficial effect of sauna therapy on endothelial and cardiac function in patients with acute heart failure or NYHA functional class IV CHF.

Conclusions

Repeated sauna treatment improves vascular endothelial function, resulting in an improvement in cardiac function and clinical symptoms.

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*1 This study was supported in part by the Scientific Research Grant from the Ministry of Education, Science and Culture of Japan.

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Journal of the American College of Cardiology
Volume 39, Issue 5, 6 March 2002, Pages 754-759