Repeated Sauna Therapy Reduces Urinary 8-Epi-Prostaglandin $F_{2\alpha}$

Akinori MASUDA,[1] MD, Masaaki MIYATA,[1] MD, Takashi KIHARA,[1] MD, Shinichi MINAGOE,[1] MD, *and* Chuwa TEI,[1] MD

SUMMARY

We have reported that repeated sauna therapy improves impaired vascular endothelial function in a patient with coronary risk factors. We hypothesized that sauna therapy decreases urinary 8-epi-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) levels as a marker of oxidative stress and conducted a randomized, controlled study. Twenty-eight patients with at least one coronary risk factor were divided into a sauna group (n = 14) and non-sauna group (n = 14). Sauna therapy was performed with a 60°C far infrared-ray dry sauna for 15 minutes and then bed rest with a blanket for 30 minutes once a day for two weeks.

Systolic blood pressure and increased urinary 8-epi-$PGF_{2\alpha}$ levels in the sauna group were significantly lower than those in the non-sauna group at two weeks after admission (110 ± 15 mmHg vs 122 ± 13 mmHg, $P < 0.05$, 230 ± 67 pg/mg · creatinine vs 380 ± 101 pg/mg · creatinine, $P < 0.0001$, respectively). These results suggest that repeated sauna therapy may protect against oxidative stress, which leads to the prevention of atherosclerosis. (Jpn Heart J 2004; 45: 297-303)

Key words: Oxidative stress, Coronary risk factors, Urinary 8-epi-prostaglandin $F_{2\alpha}$, Blood pressure, Nitric oxide (NO), Shear stress

OXIDATIVE stress is reported to increase in hypertension,[1)] hyperlipidemia,[2)] diabetes mellitus,[3)] and smoking.[4)] Oxidative stress is also known to induce gene mutations and is related to carcinogenesis.[5)] Therefore, effective control of oxidative stress is important for the prevention and treatment of such diseases. F_2-isoprostanes, namely 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$), are chemically stable products of lipid peroxidation and the urinary 8-epi-$PGF_{2\alpha}$ level has been suggested to be a reliable marker of oxidative stress *in vivo*.[6)]

We have reported that repeated sauna therapy improved vascular endothelial function in patients with coronary risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and smoking.[7)] Furthermore, we found that repeated sauna therapy upregulates mRNA and protein expression of arterial endothelial

From the [1]Department of Cardiology, Respiratory and Metabolic Medicine, Kagoshima University, Kagoshima, Japan

Address for correspondence: Chuwa Tei, MD, Department of Cardiology, Respiratory and Metabolic Medicine, Kagoshima University, 8-35-1, Sakuragaoka, Kagoshima 890-8520, Japan.

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nitric oxide synthase (eNOS) in hamsters.[8] These results suggest that the improvement of endothelial function after repeated sauna therapy may be due to improved NO production by eNOS upregulation. We hypothesized that repeated sauna therapy decreases oxidative stress and conducted a randomized controlled study to determine whether sauna therapy decreases urinary 8-epi-$PGF_{2\alpha}$ in patients with at least one coronary risk factor.

METHODS

Procedures: Spot urine samples were taken at 7 AM after an overnight fast, and the urinary 8-epi-$PGF_{2\alpha}$ level was measured by enzyme immunoassay (EIA).[9] EIA analysis provided a good correlation with negative ion chemical ionization gas chromatography/mass spectrometry analysis (NICI-GC/MS).[10] The urinary 8-epi-$PGF_{2\alpha}$ level of 20 normal healthy volunteers was 219 ± 56 pg/mg • creatinine (mean ± SD). We determined that 275 pg/mg • creatinine (mean + SD for healthy volunteers) was the cut-off value for defining a high urinary 8-epi-$PGF_{2\alpha}$ level.

Subjects: Urinary 8-epi-$PGF_{2\alpha}$ levels were measured in 94 patients with at least one coronary risk factor. There were 62 patients with levels higher than 275 pg/mg • creatinine. Twenty-eight of them agreed with our protocol and were enrolled in this study: 12 had hypercholesterolemia (> 220 mg/dL), 8 had hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg), 5 had diabetes mellitus (fasting plasma glucose >126 mg/dL), and 3 had simple obesity (body mass index, BMI > 26 kg/m^2). There were 18 smokers (> 20 cigarettes per day). The subjects were randomly divided into a sauna group (n = 14) and a non-sauna group (n = 14). There were no significant differences in age, gender, percentage of smokers, or coronary risk factors between the two groups (Table I). All patients were admitted to our hospital and ate the same meals during a two week period. Four patients in the non-sauna group and 5 patients in the sauna group were receiving medications, such as antihypertensive drugs and hypolipidemic drugs. There were no differences in the medications with respect to HMG-CoA reductase inhibitors, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blocker between the two groups. The duration of administration was 12 ± 6 months (mean ± SD). Their medications had not been changed for at least two weeks before and during this study. None of the patients had coronary artery disease. Written informed consent was obtained from all patients before participation, and the study protocol was approved by the Ethics Committee of the Faculty of Medicine, Kagoshima University.

Measurements: Body weight, heart rate, blood pressure, hematocrit, total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose, and urinary 8-epi-

Table I. Patient Characteristics

	Non-sauna group (n = 14)	Sauna group (n = 14)
Age, yr	40 ± 14	43 ± 17
Sex, Male/Female	7 / 7	7 / 7
Risk factor		
Smoking, n	8	10
Hypertension, n	4	4
Hypercholesterolemia, n	6	6
Diabetes mellitus, n	3	2
Simple obesity, n	1	2
Medications, n	4	5
HMG-CoA, n	4	3
ACE-I, n	2	2
ARB, n	1	2

HMG-CoA = HMG-CoA reductase inhibitor; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

PGF$_{2\alpha}$ levels were measured on admission and two weeks after admission. Fasting blood was obtained at 7 AM after an overnight fast.

Sauna therapy: A far infrared-ray dry sauna (Olympia Co., Miyazaki, Japan) was performed as previously reported.[6,11,12] The patients in the sauna group were placed in a supine position in a 60°C sauna for 15 minutes, and once removed, allowed to rest on a bed in a supine position with a blanket to keep them warm for an additional 30 minutes. The patients were weighed before and after the sauna therapy; oral hydration with water was used to compensate for lost weight. The therapy was performed once a day for two weeks. The non-sauna group patients were placed in a supine position in a temperature-controlled (24°C) room for 45 minutes once a day.

Statistical analysis: All values are given as the mean ± SD. Statistical comparisons were made with the Student two-tailed group t-test (sauna group and non-sauna group) and two tailed paired t-test (on admission and two weeks after admission). P values of less than 0.05 were considered statistically significant.

RESULTS

Body mass index, heart rate, blood pressure, hematocrit, total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose, and urinary 8-epi-PGF$_{2\alpha}$ levels on admission were not significantly different between the two groups. Systolic blood pressure in the sauna group decreased significantly after two weeks of sauna therapy and it was significantly lower than that of the non-sauna group at

Table II. Changes in Clinical Parameters in Patients with Increased Urinary 8-Epi-$PGF_{2\alpha}$

	Non-sauna group (n = 14)		Sauna group (n = 14)	
	on admission	2 weeks after admission	on admission	2 weeks after admission
Body mass index (kg/m^2)	24 ± 6	24 ± 3	24 ± 5	23 ± 7
Heart rate (beats/min)	74 ± 12	73 ± 11	72 ± 9	73 ± 12
Systolic blood pressure (mmHg)	125 ± 15	122 ± 13	125 ± 13	110 ± 15 *†
Diastolic blood pressure (mmHg)	78 ± 12	80 ± 9	76 ± 9	74 ± 12
Hematocrit (%)	47 ± 3	48 ± 2	46 ± 4	47 ± 3
Total cholesterol (mg/dL)	207 ± 63	207 ± 59	191 ± 50	188 ± 36
HDL cholesterol (mg/dL)	48 ± 13	47 ± 11	51 ± 15	49 ± 13
Triglycerides (mg/mL)	198 ± 190	173 ± 115	138 ± 105	145 ± 40
Fasting plasma glucose (mg/dL)	107 ± 28	109 ± 25	92 ± 15	93 ± 17

Systolic blood pressure in the sauna group significantly decreased after two weeks of sauna therapy (*$P < 0.05$) and it was significantly lower than that of the non-sauna group at two weeks after admission (†$P < 0.05$). Mean ± SD, *$P < 0.05$ compared with on admission in sauna group. †$P < 0.05$ compared with 2 weeks after admission in non-sauna group.

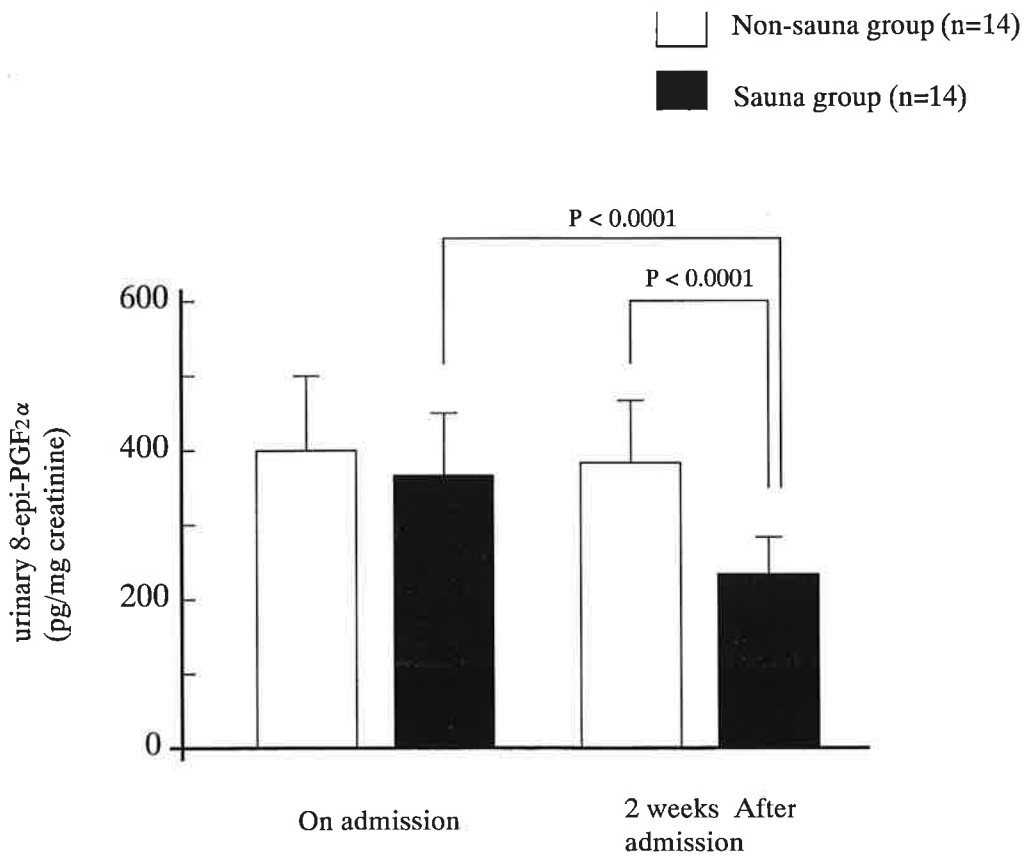

Figure. Urinary 8-epi-$PGF_{2\alpha}$ levels on admission and 2 weeks after admission in the sauna group (solid columns) and non-sauna group (open columns).
The urinary 8-epi-$PGF_{2\alpha}$ level in the sauna group significantly decreased after two weeks of sauna therapy and it was significantly lower than that of the non-sauna group at two weeks after admission.

two weeks after admission (110 ± 15 mmHg vs 122 ± 13 mmHg, $P < 0.05$) (Table II). There were no significant differences in BMI, heart rate, diastolic blood pressure, hematocrit, total cholesterol, HDL cholesterol, triglycerides, and fasting plasma glucose between the two groups at two weeks after admission.

The urinary 8-epi-PGF$_{2\alpha}$ level in the sauna group was significantly decreased after two weeks of sauna therapy and it was significantly lower than that of the non-sauna group at two weeks after admission (230 ± 67 pg/mg • creatinine vs 380 ± 101 pg/mg • creatinine, $P < 0.0001$, Figure). No patient reported feeling ill during the sauna therapy.

DISCUSSION

We found that repeated sauna therapy decreases systolic blood pressure and increases urinary 8-epi-PGF$_{2\alpha}$. Winterfeld, *et al*[13] investigated the effects of regular sauna bathing on blood pressure and found that a 3-month period of biweekly sauna bathing lowered mean blood pressure from 166/101 to 143/92 mmHg in 46 hypertensive patients. In our studies, the systolic blood pressure in patients with coronary risk factors[7] and CHF patients[14] significantly decreased after two weeks of sauna therapy. We observed that endothelial function in the brachial artery improved after two weeks of sauna therapy. Furthermore, systemic vascular resistance decreased after two weeks of sauna therapy, suggesting an improvement of endothelial function in resistance vessels.[14] Decreased systolic blood pressure in repeated sauna therapy may reflect an improvement in endothelial function.

Oxidative stress has been reported to have an important correlation with some diseases such as atherosclerosis,[15] cancer,[5] and Alzheimer's disease.[16] However, prospective controlled clinical trials of antioxidants have not provided a consensus view. The CHAOS study showed that the administration of vitamin E benefited patients with coronary artery disease,[17] whereas the HOPE study and GISSI-Prevenzione study did not find vitamin E to be useful.[18,19] We found that the increased urinary 8-epi-PGF$_{2\alpha}$ in the sauna group was significantly lower than that of the non-sauna group at two weeks after admission. All patients had the same meals during this study, which probably did not differ in their antioxidant contents. This finding indicates that repeated sauna therapy may have the effect of reducing increased urinary 8-epi-PGF$_{2\alpha}$ levels. In the absence of a consensus view on the effects of antioxidants, repeated sauna therapy may be expected to be an effective method with which to reduce oxidative stress.

8-epi-PGF$_{2\alpha}$ causes a dose-dependent vasoconstriction in coronary strips obtained from normal and hypercholesterolemic pigs. Coronary vasoconstriction induced by 8-epi-PGF$_{2\alpha}$ has been shown to be modulated by endothelial nitric

oxide (NO).[20] Repeated sauna therapy increases cardiac output and peripheral blood flow, which increases shear stress in vessels.[7,14] The increased shear stress leads to an increase in NO production by the vessels. NO dilates blood vessels and inhibits platelet aggregation, and prevents the onset and progression of atherosclerosis. These observations suggest that repeated sauna therapy may have the effect of improving vascular endothelial function by increasing NO production through increased shear stress, and that sauna therapy prevents atherosclerosis by reducing 8-epi-$PGF_{2\alpha}$ levels.

Roberts, *et al*[21] reported that unrestricted consumption of a low-fat, high-fiber diet with daily exercise resulted in dramatic improvements in blood pressure, oxidative stress, NO availability, and the metabolic profile within 3 weeks in obese men. Repeated sauna therapy can be used even for patients who are unable to exercise. We have not observed the symptomatic deterioration of patients during or after sauna therapy. We suggest that the combination of diet, exercise, and repeated sauna therapy may be the best method for preventing lifestyle related diseases such as hypertension, hyperlipidemia, and diabetes mellitus.

Laminar shear stress upregulates the expression of superoxide dismutase (SOD) and glutathione peroxidase (GPX) in endothelial cells.[22] SOD converts superoxide anion to H_2O_2, and H_2O_2 is reduced by GPX. Though we did not examine SOD and GPX in this study, the reduction in urinary 8-epi-$PGF_{2\alpha}$ by repeated sauna therapy may be related to the increase in shear stress.

In conclusion, repeated sauna therapy decreased blood pressure and increased urinary 8-epi-$PGF_{2\alpha}$ in patients with at least one coronary risk factor. These results suggest that repeated sauna therapy may have a preventive effect in terms of atherosclerosis. Further studies are needed to investigate the beneficial effect of long-term repeated sauna therapy on the prevention of lifestyle-related diseases and outcomes of patients with coronary risk factors.

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