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Repeated Sauna Treatment Improves Vascular Endothelial and Cardiac Function in Patients With Chronic Heart Failure

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OBJECTIVES The purpose of this study was to determine the mechanism by which 60°C sauna treatment improves cardiac function in patients with chronic heart failure (CHF).

BACKGROUND We have previously reported that repeated 60°C sauna treatment improves hemodynamic data and clinical symptoms in patients with CHF. We hypothesized that the sauna restores endothelial function and then improves cardiac function.

METHODS Twenty patients (62 ± 15 years) in New York Heart Association (NYHA) functional class II or III CHF were treated in a dry sauna at 60°C for 15 min and then kept on bed rest with a blanket for 30 min, daily for two weeks. Ten patients with CHF, matched for age, gender and NYHA functional class, were placed on a bed in a temperature-controlled (24°C) room for 45 min as the nontreated group. Using high-resolution ultrasound, we measured the diameter of the brachial artery at rest and during reactive hyperemia (percent flow-mediated dilation, %FMD: endothelium-dependent dilation), as well as after sublingual administration of nitroglycerin (%NTG: endothelium-independent dilation). Cardiac function was evaluated by measuring the concentrations of plasma brain natriuretic peptide (BNP).

RESULTS Clinical symptoms were improved in 17 of 20 patients after two weeks of sauna therapy. The %FMD after two-week sauna treatment significantly increased from the baseline value, whereas the %NTG-induced dilation did not. Concentrations of BNP after the two-week sauna treatment decreased significantly. In addition, there was a significant correlation between the change in %FMD and the percent improvement in BNP concentrations in the sauna-treated group. In contrast, none of the variables changed at the two-week interval in the nontreated group.

CONCLUSIONS Repeated sauna treatment improves vascular endothelial function, resulting in an improvement in cardiac function and clinical symptoms. (J Am Coll Cardiol 2002;39:754–9)

In patients with chronic heart failure (CHF), clinical symptoms due to reduced peripheral perfusion, such as muscle fatigue, heaviness in the limbs, edema, appetite loss and constipation, are often observed (1). The sympathetic nerve and renin-angiotensin system is activated to compensate for a reduced cardiac output in CHF, resulting in increased afterload and reduced peripheral perfusion (2). Vasodilators, such as angiotensin-converting enzyme inhibitors, improve CHF largely by increasing peripheral perfusion (3). We have applied thermal therapy through the sauna, which also increases cardiac output and peripheral perfusion (4,5), to patients with CHF and have found that thermal therapy improves hemodynamic variables (5) and clinical symptoms (6) in many of these patients. Experimental studies have demonstrated that CHF impairs endothelial-dependent vasodilation of canine femoral arteries (7) and rat hind-limb resistance vessels (8) in response to acetylcholine, and in humans, peripheral resistance vessels and large conduit vessels are also impaired in CHF (9–12). One of the proposed mechanisms by which this occurs is through decreased peripheral vascular production of endothelium-derived nitric oxide (NO) in an animal model of CHF (13) and in patients with CHF (14,15). This may occur because of decreased shear stress due to reduced peripheral perfusion (16). Shear stress is an important stimulus for NO production (17–19) and the expression of endothelial NO synthase (eNOS) (20,21). Furthermore, several studies have shown that endothelial function in patients with CHF is improved by treatment with L-arginine (22,23), treatment with angiotensin-converting enzyme inhibitors (24,25), physical training (26), administration of dobutamine (27) or oral treatment with vitamin C (28). However, it remains unproved whether restoration of endothelial function can improve cardiac function in patients with CHF. Because thermal therapy increases cardiac output and improves peripheral perfusion in patients with CHF (5), we hypothesized that thermal therapy improves

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Abbreviations and Acronyms

ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CHF = chronic heart failure
CTR = cardiothoracic ratio
eNOS = endothelial nitric oxide synthase
%FMD = percent flow-mediated dilation
LVEDD = left ventricular end-diastolic dimension
NO = nitric oxide
%NTG = percent nitroglycerin
NYHA = New York Heart Association
TBARS = thiobarbituric acid-reactive substances
TNF = tumor necrosis factor

peripheral vascular endothelial function, resulting in improved cardiac function.

METHODS

Study group. We studied 20 patients (age range 30 to 75 years, mean 62 ± 15 years) with CHF; 17 of them (9 men and 8 women) had idiopathic dilated cardiomyopathy and 3 (all men) had ischemic cardiomyopathy. Ten patients were in New York Heart Association (NYHA) functional class II, and the other 10 patients were in class III. The mean cardiothoracic ratio (CTR) on chest radiography was 58 ± 7% (range 49% to 75%). The mean left ventricular ejection fraction on echocardiography was 38 ± 14% (range 15% to 54%). Ten patients with CHF, matched for age, gender and NYHA functional class, were included in this study as the nontreated group. All patients were receiving maintenance doses of medications for heart failure, such as angiotensin-converting enzyme inhibitors, diuretics and, in most cases, beta-blockers and digitalis, and they were in stable clinical condition for one month before study entry. Their medications had not been changed for at least two weeks before and during this study. Written, informed consent was obtained from all patients before participation, and the protocol was approved by the Ethics Committee of the Faculty of Medicine, Kagoshima University.

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

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

	Sauna-Treated Group (n = 20)			Nontreated Group (n = 10)			Comparison at Baseline
	Baseline	After 2 Weeks	p Value	Baseline	After 2 Weeks	P Value	p Value
Age (yrs)	62 ± 15			64 ± 16			0.74
Gender (M/F)	12/8			6/4			1.0
DCM/ICM	17/3			8/2			0.73
NYHA functional class (I/II/III)	0/10/10	1/14/5	0.01	0/5/5	0/5/5	1.0	1.0
Body weight (kg)	53.5 ± 12.3	53.3 ± 12.2	0.52	60.8 ± 16.2	61.8 ± 15.6	0.42	0.18
SBP (mm Hg)	107 ± 22	97 ± 17	0.019	112 ± 14	111 ± 14	0.87	0.52
DBP (mm Hg)	63 ± 13	61 ± 10	0.40	67 ± 6	67 ± 14	1.0	0.26
Heart rate (beats/min)	71 ± 13	70 ± 11	0.61	68 ± 14	67 ± 14	0.66	0.57
CTR (%)	58.2 ± 7.1	55.9 ± 7.9	0.002	56.2 ± 4.4	56.3 ± 4.5	0.59	0.42
LVEDD (mm)	59 ± 8	57 ± 9	0.047	60 ± 7	59 ± 8	0.42	0.74
LAD (mm)	46 ± 9	45 ± 10	0.17	41 ± 8	41 ± 8	0.18	0.15
Ejection fraction (%)	38 ± 14	39 ± 12	0.78	32 ± 13	31 ± 12	0.73	0.27
Norepinephrine (pg/ml)	426 ± 234	432 ± 333	0.91	464 ± 185	467 ± 259	0.97	0.66
Epinephrine (pg/ml)	31 ± 36	32 ± 34	0.94	28 ± 13	29 ± 19	0.84	0.74
Dopamine (pg/ml)	12 ± 30	11 ± 35	0.31	14 ± 13	14 ± 10	0.89	0.80
ANP (pg/ml)	107 ± 101	90 ± 94	0.34	111 ± 104	116 ± 112	0.75	0.92
BNP (pg/ml)	441 ± 444	293 ± 302	0.005	434 ± 420	454 ± 396	0.64	0.97
TBARS (pg/ml)	2.6 ± 1.1	2.6 ± 1.3	0.89	2.8 ± 0.9	3.0 ± 0.9	0.42	0.81
TNF-alpha (pg/ml)	1.4 ± 0.8	1.6 ± 1.7	0.65	1.4 ± 1.8	1.3 ± 1.6	0.90	0.65
%FMD (%)	4.4 ± 2.5	5.7 ± 2.5	0.0006	4.5 ± 1.9	4.4 ± 1.9	0.69	0.91
%NTG-induced dilation (%)	19.2 ± 6.5	18.7 ± 6.9	0.61	18.0 ± 5.4	17.1 ± 5.3	0.33	0.42
Hyperemia (%)	478 ± 209	417 ± 261	0.20	500 ± 325	473 ± 191	0.73	0.83

*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.

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).

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

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

Patient No.	Diagnosis	Age (yrs)/ Gender	NYHA Functional Class	CTR (%)	LVEDD (mm)	BNP (pg/dl)		%FMD (%)		Clinical Symptoms
						Before Sauna Therapy	After 2 Weeks of Sauna Therapy	Before Sauna Therapy	After 2 Weeks of Sauna Therapy	
1	DCM	77/F	III	62	52	258	207	5.4	6.4	Improved
2	DCM	75/F	III	64	58	595	593	9.9	10.0	Improved
3	DCM	74/F	II	66	59	89	75	5.5	5.1	Improved
4	DCM	50/F	II	63	56	82	49	10.4	11.6	Improved
5	DCM	39/M	II	54	70	51	41	2.4	3.0	Improved
6	DCM	70/M	III	49	66	1,960	1,230	4.7	5.0	Improved
7	DCM	68/F	II	65	67	377	222	4.9	7.7	Improved
8	DCM	58/M	II	50	60	215	123	4.6	6.7	Improved
9	DCM	62/M	III	60	72	998	879	5.1	5.0	Unchanged
10	DCM	44/M	III	63	59	548	434	5.3	4.9	Unchanged
11	DCM	80/F	III	75	58	475	187	4.2	8.0	Improved
12	DCM	75/M	II	53	56	278	221	6.7	8.3	Improved
13	ICM	57/M	II	45	52	46	48	2.3	2.2	Unchanged
14	DCM	70/F	II	57	52	183	60	3.1	4.4	Improved
15	DCM	58/M	III	55	60	304	228	2.3	4.4	Improved
16	DCM	60/F	III	55	48	200	92	3.9	5.4	Improved
17	DCM	72/M	II	55	53	315	347	4.2	3.7	Improved
18	ICM	72/M	II	54	55	438	351	2.1	3.6	Improved
19	DCM	33/M	III	66	78	939	249	0.6	2.5	Improved
20	ICM	73/M	III	56	52	468	229	1.3	5.1	Improved

Abbreviations as in Table 1.

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).

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).

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 concentra-

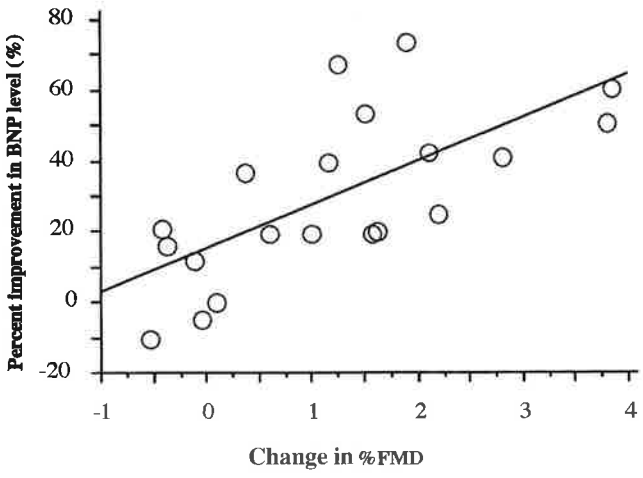

Figure 1. Relationship between the change in percent flow-mediated dilation (%FMD) and the percent improvement in brain natriuretic peptide (BNP) concentration in the sauna-treated group. There is a positive correlation between the change in %FMD and the percent improvement in BNP concentration before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

tions. Recent studies have indicated that plasma BNP concentrations are an important marker of cardiac status and prognosis in patients with heart failure (30–32). 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 (9–12). 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 (39,40). 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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