Leg Heating Using Far Infra-red Radiation in Patients with Chronic Heart Failure Acutely Improves the Hemodynamics, Vascular Endothelial Function, and Oxidative Stress

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Abstract

Background Systemic thermal therapy (STT) has been associated with beneficial effects in patients with chronic heart failure (CHF). The fact, however, that it requires a dedicated as well as spacious facility and trained personnel makes it difficult to practice in the daily care of patients with CHF.

Objective The aim of this study was to determine whether the leg thermal therapy (LTT) has a positive impact similar to that of STT in patients with CHF.

Methods and Results Twenty patients with CHF (57±17 years old, left ventricular ejection fraction=30±10%) received LTT (45°C) for 20 minutes. Immediately after the treatment, the core temperature had increased (+0.3±0.3°C) (p<0.01). While the LTT had no significant effects on the heart rate, systolic arterial pressure, and diastolic blood pressure, it increased the cardiac output (mixed venous oxygen saturation; +2±3%) and decrease the pulmonary capillary wedge pressure (-2±2 mmHg). The LTT significantly improved the flow-mediated vasodilatation (FMD) from 4.8±2.6 to 7.1±3.6%, the antioxidative markers, thiol from 4.0±0.7 to 4.5±0.9 μmoL/g, and the marker of oxidative deoxyribonucleic acid (DNA) damage, urine 8-hydroxy-2'deoxyguanosine (8OHdG) from 100 to 82±3%, respectively (p<0.05). No patient had any adverse effects associated with LTT.

Conclusion LTT acutely improved FMD, and oxidative stress in patients with CHF. Although the long-term effect of LTT remains to be investigated, its practicality which is comparable to that of STT would make it an attractive therapeutic strategy for patients with CHF.

Key words: heart failure, thermal therapy, endothelial function, oxidative stress

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Introduction

Systemic thermal therapy (STT), so-called Sauna or warm water insertion therapy (1), which is considered to be one of the thermal vasodilatation therapies and has been applied to many healthy people for centuries, has been gathering attention from various medical fields. There have been reviews of the physiologic effects, benefits and risks of sauna bathing (2, 3). It seems that the risks of sauna have been empha-sized in people without chronic heart failure (CHF) (4), and thus many patients with CHF do avoid sauna because of those risks or adverse effects. However, sauna bathing may be a beneficial therapeutic option for patients with hypertension, CHF, or coronary artery disease (5-8). The common mechanism of the action might be improvement in vascular endothelial function which results in a reduced cardiac preload and afterload (2).

Tei and colleagues have introduced a supervised dry sauna at 60°C and have shown that hyperthermia appeared...
to improve left ventricular function and vascular activity in people with CHF (5-9). In addition, many people, even patients with CHF, have found sauna bathing pleasurable and relaxing (9). Thermal therapy may be an alternative or adjuvant treatment for patients with CHF which provides not only cardiovascular benefits but also relaxation and pleasure.

Currently thermal vasodilatation therapies have limited use because they need certain facilities and supervisors for sauna treatment. Because of this limitation sauna therapy cannot be performed at home and patients who would benefit from the sauna therapy would have to be limited to hospitals or special places capable of providing such facilities. If we can expand the possibility of thermal therapy as to be performed at patients’ homes, then it would really be an alternative or adjuvant therapy for CHF. Thus, we looked into the possibility of leg thermal therapy (LTT) as one of the thermal vasodilatation therapies and studied its general effects on cardiovascular dynamics and on other factors closely related to CHF.

**Materials and Methods**

**Study population and laboratory analysis** (Table 1)

Twenty patients with CHF (13 males and 7 females with a mean age of 57±17 years) underwent LTT at our hospital. To be included into the study the patients had to have a history of congestive heart failure with New York Heart Association (NYHA) functional class II to III symptoms. Ten of them had dilated cardiomyopathy, 1 hypertensive heart disease, 3 hypertrophic cardiomyopathy (dilated phase) and 2 ischemic heart disease, cardiac sarcoidosis, or cardiac amyloidosis. The basic heart rhythm of 19 patients was sinus rhythm, and that of only 1 patient was atrial fibrillation. Two of them underwent implantation of cardiac resynchronization therapy with intrinsic p wave and paced QRS wave. All patients’ left ventricular ejection fraction by echocardiography was less than 50%. All patients received appropriate medical therapy for their CHF including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor antagonists, beta-adrenergic receptor antagonists, and diuretics. Their medications were not changed during the study. All patients were in a stable clinical condition for at least 1-month before study entry. The study protocol was approved by the Ethics Committee of the Faculty of Medicine in Kyushu University, and written informed consent was obtained from all patients before the study.

**Protocol of the LTT**

All patients were placed in a supine position on a bed in a temperature-controlled room at 25°C. In order to exclude the effect of simply rest, they took bed rest for at least 30 minutes. After evaluation of flow-mediated vasodilatation (FMD) as described below, they received leg heating with far infra-red radiation (Leghot®, Fujika Co., Ltd., Tokyo, Japan) at 45°C for 20 minutes, and then, remained in bed at rest with a blanket to keep them warm for an additional 30 minutes (Fig. 1). In order to exclude the possibility of the benefits of such a bed rest without LTT on CHF, we evaluated the FMD after bed rest for 50 minutes without LTT (n=5).

**Evaluation of the hemodynamic parameters**

The hemodynamic data including the pulmonary capillary wedge pressure (PCWP), mixed venous oxygen saturation (SvO2) which is an indicator of the cardiac output, and right atrial pressure were monitored by a Swan-Ganz catheter (Edwards Lifesciences Co., Ltd., Tokyo, Japan) inserted into the right jugular vein, and the heart rate and arterial blood pressure (Life Scope LT, Nihon Cohden Co., Ltd., Tokyo, Japan) were measured before and after the LTT (Fig. 1). The body core temperature was measured by a Swan-Ganz catheter placed in the pulmonary artery and skin temperature sensors (CoretempCM-210, TERUMO Corporation, Tokyo, Japan) placed on the forehead and chest. The amount of sweating was evaluated from the body weight measurements before and during the LTT. All the patients drank 300 milliliters of water to compensate for the loss of weight before and during the LTT.

**Heart rate variability (HRV) analysis**

The HRV was analyzed using a commercial software program (NI Labview, National Instruments Corporation, Tokyo, Japan) as previously described (10). The following frequency-domain measurements were assessed: 1) low frequency; LF (0.05 to 0.15 Hz), 2) high frequency; HF (0.15 to 0.50 Hz), and 3) LF/HF ratio. The LF power reflected the sympathetic and parasympathetic modulation of the heart rate, whereas the HF power mainly reflected the vagal modulation (11). The LF and HF measurements were reported as their natural logs (ln). The data were also analyzed by correcting the LF and HF components for the total power (0.0 to 1.0 Hz). The frequency-domain measurements were
Figure 1. Setup of the leg thermal therapy for patient with chronic heart failure. LTT and FMD indicate leg thermal therapy and flow-mediated vasodilation, respectively.

Laboratory measurements

30 minutes following complete bed rest before the LTT and after the LTT, blood and urine samples were obtained to evaluate the serum level of the neurohormonal factors including the serum human atrial natriuretic peptide (hANP), brain natriuretic peptide (BNP), ACE activity, plasminogen activator inhibitor-1 (PAI-1), highly sensitive C-reactive protein (hs-CRP), and urine catecholamines including norepinephrine (NEP), epinephrine (EP), and dopamine (DOPA). The serum hANP and BNP were measured with a radioimmunoassay. The serum ACE activity was determined using a fluorometric assay. The hs-CRP was measured with a clinically validated high-sensitivity assay. The plasminogen activator inhibitor (PAI-1) was measured with enzyme-linked immunosorbent assays (ELISA). The urine catecholamines were measured with high-performance liquid chromatography. The degree of lipid peroxidation was determined in the blood sample through biochemical assay of thiobarbituric acid-reactive substances (TBARS) (12, 13). The plasma was mixed with 0.1 mol/L H2SO4 and 1% phosphotungstic acid, and the mixture was centrifuged. The sediment was suspended in distilled water, 1% thiobarbituric acid, and 0.1% butylated hydroxytoluene. The reaction mixture was then heated at 100°C for 60 minutes in an oil bath. After the mixture was cooled with tap water, it was extracted with n-butanol and centrifuged at 1,600 g for 15 minutes. The fluorescence intensity of the organic phase was measured by use of a spectrofluorometer with a wavelength of 515-nm excitation and 553-nm emission. Malondialdehyde standards (Sigma Chemical Co., St. Louis, MO, USA) were included with each assay batch, and plasma TBARS were expressed as nanomoles per milliliter of plasma in reference to these standards. Urine samples were centrifuged at 2,000 rpm for 10 minutes and the supernatants were used for assay. Concentration of 8-OHdG in each urine sample was determined by using a competitive enzyme-linked immunosorbent assay kit (8-OHdG check, Japan Institute for the Control of Aging, Nagoya, Japan). Each value was corrected by urinary creatinine measured by a colorimetric assay kit based on color reactions between creatinine and picroate (Sigma). Concentration of urinary 8-OHdG was calculated as ng/mg of creatinine. Plasma thiols were assayed according to the method described by Ellman (14). Ellman’s reagent 5,5’-dithiobis-2-nitrobenzoic acid (DTNB) (Wako Pure Chemical Industries, Inc., Osaka, Japan) was added and samples were incubated at 37°C for 15 minutes. The absorbance was read at 412 nm against a reagent blank. Results were calculated using a molar extinction coefficient of yellow anion ($\varepsilon = 13,600$). Glutathione peroxidase (GPx) activities were examined by following the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) in the presence of Glutathione (GSH) reductase, which catalyzes the reduction of oxidized GSH formed by GPx. Both samples and reference cuvettes contained 0.1 M Tris-HCl, pH 7.4, 0.2 mM nicotinamide adenine dinucleotide phosphate (NADPH), 0.5 mM 2-{2-[bis(carboxymethyl)amino]ethyl} (carboxymethyl) amino) acetic acid (EDTA), 2 mM GSH, and 1 unit of GSH reductase in a total volume of 1 mL. An aliquot of each enzyme was added to the sample cuvette only. The reaction mixture was preincubated at 37°C for 2 minutes, after which the reaction was started by the addition of peroxide to both cuvettes. The oxidation of NADPH was followed at 340 nm at 37°C, and activity was expressed as micromoles of NADPH oxidized per minute. The serum vascular endothelial growth factor (VEGF) was measured using Quantikine sandwich (ELISA; R&D Systems, Minneapolis, MN, USA) (15).

Assessment of the endothelial function

The endothelial-dependent vascular reactivity was indexed by a direct assessment of the brachial artery FMD. Changes
in the brachial artery diameter during reactive hyperemia were measured by high-resolution ultrasound (Philips iE33, Philips Electronics Japan Co., Ltd., Tokyo, Japan) as previously described in detail (16, 17). Briefly, after the 30 minutes rest in the supine position before and after the LTT, an FMD measurement was performed with a 7.5-MHz linear-array ultrasound probe (Philips iE33L11-3, Philips Electronics Japan Co., Ltd., Tokyo, Japan). Increased blood flow was induced by a blood pressure cuff placed around the forearm, with a 5-minute inflation at 50 mmHg above the subject’s systolic blood pressure, followed by rapid deflation. Baseline images before the cuff inflation and then for 2 minutes after the cuff deflation were recorded. The arterial diameter was measured in the end-diastolic phase from the recordings. The imaging and analysis were performed by a single observer blinded to the subject’s identity. Measurements were taken from the anterior to posterior interface between the media and adventitia. Every 5 cardiac cycles of measurement from 60 to 120 seconds for the baseline and from 30 to 240 seconds after the cuff deflation (hyperemia) were taken. For the reactive hyperemia response, the measurements with the 5 largest diameters were averaged, and the percent increase from baseline was determined as the %FMD. Endothelium-independent vasodilation was evaluated after the sublingual administration of 0.4 mg of nitroglycerin, an exogenous nitric oxide (NO) donor. The brachial diameter and blood pressure were measured before and 3 to 4 minutes after the nitroglycerin administration.

### Statistical analysis

The numerical results are expressed in the text as the mean ± standard deviation. Statistical analysis was performed using a Student t test or two-way Analysis of Variance (ANOVA) for the comparison of 2 groups. A value of p<0.05 was considered to indicate statistical significance.

### Results

**Study population and laboratory analysis (Table 1)**

Before the LTT, the mean NYHA functional class was 2.8±0.6 and the left ventricular ejection fraction (LVEF), assessed by echocardiography, was decreased to 30±10%, with an increased serum BNP, measured in a stable clinical condition, which was increased to 611±607 pg/dL. Lastly, peak oxygen consumption (peak VO2), measured by cardiopulmonary exercise test, was 16±4 mL/kg/min. These findings indicate that all patients had mild to moderate CHF.

**Hemodynamic parameters and the HRV (Table 2)**

The LTT steadily elevated not only systemic body temperature but also the body core temperature by 0.3±0.3 °C compared with before (p<0.01), and that elevation continued for at least 30 minutes after the leg heating was terminated. The amount of sweating was 222±174 milliliters during the LTT. The LTT comparably decreased the heart rate (-3±6 beats per minute), systemic arterial pressure (-2.3±11 mmHg), and PCWP (-2.3±1.9 mmHg), and increased the SvO2 (+2±3%) compared with before the LTT, respectively. Although the cardiac amyloidosis and sarcoidosis are potentially at high risk of hypotension, LTT was safely performed for these patients without any adverse effects. The LTT did not significantly change the LF/HF ratio compared with before the LTT.

**Neurohormonal factors and oxidative stress markers**

The treatment with the LTT did not affect the neurohormonal factors, as measured by the change in the hANP (102±37%), ACE (94±11%), PAI-1 (102±32%), and hs-CRP (103±11%) serum levels (Fig. 2A). The LTT tended to decrease the urine catecholamines including the NEP (90±37%), EP (91±33%), and dopamine (DOPA) (94±41%) but the decrease was not statistically significant (Fig. 2A). On the other hand, the LTT significantly increased the serum antioxidative stress marker, Thiol (4.0±0.7 vs. 4.5±0.9

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### Table 2. Hemodynamic Parameters and Heart Rate Variability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After LTT</th>
<th>changes from baseline of the parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body core temperature (°C)</td>
<td>36.2±0.4</td>
<td>36.5±0.4</td>
<td>+0.3±0.3*</td>
</tr>
<tr>
<td>Amount of sweating (ml)</td>
<td></td>
<td>222±174</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>74±22</td>
<td>70±18</td>
<td>-3±6</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>88±10</td>
<td>90±17</td>
<td>+2.3±11</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>52±9</td>
<td>52±15</td>
<td>+0.4±12</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>26.0±11.0</td>
<td>23.7±8.7</td>
<td>-2.3±1.9 (n=3)</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>10.0±3.6</td>
<td>9.7±3.5</td>
<td>-0.3±1.2 (n=3)</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>60.3±4.5</td>
<td>62.0±7.2</td>
<td>+2.0±3.0 (n=3)</td>
</tr>
<tr>
<td>Heart Rate Variability (LF/HF)</td>
<td>1.1±0.9</td>
<td>1.0±0.7</td>
<td>-0.14±0.5</td>
</tr>
</tbody>
</table>

n=20, *p<0.01 compared with before the leg thermal therapy, HF: High Frequency, LF: Low Frequency
Figure 2. The leg thermal therapy (LTT) did not affect the neurohormonal factors including the serum human atrial natriuretic peptide (hANP), angiotensin-converting enzyme (ACE), plasminogen activator inhibitor (PAI)-1, highly sensitive C reactive protein (hs-CRP), and urine norepinephrine (NEP), epinephrine (EP), and dopamine (DOPA) levels (A). The LTT significantly increased the serum antioxidative stress marker, sulfhydryl content (Thiol) and significantly decreased the urine 8-hydroxy-2’deoxyguanosine (8OHdG) (D), but not the serum Glutathione peroxidase (GPx) (B) and the thiobarbituric acid-reactive substances (TBARS) (C). The LTT tended to increase vascular endothelial growth factor (VEGF) (E). The open and closed bars indicate the levels before and after the LTT, respectively. *p<0.05 vs. before LTT.

Effect on the endothelial function

At baseline, the brachial artery diameter increased in all subjects in response to the reactive hyperemia, however, that increase was much less, compared to the reported normal range (17). For all subjects, the mean FMD after the LTT (7.1±3.6%) significantly increased compared to that before (4.8±2.6%, p<0.01, Fig. 3). These significant improvements in the FMD with the LTT were similar to those with STT as previously described (6). The baseline diameter of the studied artery was not affected by the LTT. Also, the nitroglycerin-induced vasodilation was similar before and after the LTT. The bed rest for 50 minutes without LTT did not affect FMD (5.6±2.4% vs. 5.3±2.4%).

Discussion

Despite the major advances in the pharmacologic, medical devices, and surgical treatment of CHF, the mortality and morbidity still remain high (18). Thus, the search for effective and safe modalities continues. One approach that has attracted attention is STT, which utilizes relatively small increases in the core body temperature intermittently for therapeutic purposes. Previous reports revealed that a significant improvement using STT was noted across many CHF-related parameters, including the endothelial function (5, 6), hemodynamics (19), cardiac geometry (20), neurohormonal markers (6), oxidative stress (21, 22), quality of life and
The precise mechanisms of the beneficial effects of STT have not been fully clarified, yet we speculated that the reduction in the preload and afterload of the heart due to thermal vasodilatation, and the elevation in the core body temperature were two essential factors. Further, we presumed that patients with CHF might benefit from partial body warming if it could raise the core body temperature and if it could cause thermal venous vasodilatation sufficient to reduce the venous return and peripheral arterial vasodilatation which would lead to a reduction in the arterial resistance. If we could achieve a similar effect as STT by warming the lower extremities, then it would benefit the patients with moderate to severe CHF who have to stay in bed. In addition, the type of facilities for warming the patients would be simpler than those for systemic warming with a sauna bath, which would definitely have a financial benefit. For example, an electrical warming blanket might be of some use in partial body warming, which many hospitals are surely equipped with.

We decided to apply the use of a far infra-red radiant heater to the patients’ legs for the following reasons. First, it is made for use in the home and has a safety qualification; SG: Safety Goods mark from the Consumer Product Safety Association (CPSA), Japan. Also, far infra-red radiant heaters are more efficient than heaters using heat conduction. Secondly, there was a report on the LTT, which proved that it increases the core body temperature (24).

The effects of partial body warming from LTT were smaller than those reported for STT, and the rise in the core body temperature was 0.3 degrees on average, whereas STT induced a 1°C rise in the core body temperature. However, it still brought about favorable changes in the systemic arterial pressure, heart rate (HR), PCWP, and SvO2. This suggests that patients with CHF may benefit from partial body warming though the efficacy of the LTT may fall short of that of STT. However, the side effects of partial thermal therapy may be fewer than those for STT, because the heat is applied to only a part of the body. The temperature during the experiment was set to 45 degrees which was comparatively low for a sauna bath. We did not experience any adverse effects of the LTT throughout the experiment. Moreover, the LTT improved the oxidative stress and endothelial function which is equivalent to that for STT as previously described (6).

**Endothelial function and oxidative stress**

Some studies have demonstrated that endothelial function decreases in patients with CHF (25, 26), and the mechanism has been proposed to be a decreased NO bioavailability associated with increased NADPH oxidase, which is an important source of oxidative stress-derived superoxide generation (27-29). Another study demonstrated that STT-induced attenuation of vascular densities was associated with the upregulation of endothelial NO synthesis and VEGF expression in the noninfarcted myocardium (30). In the present study, we demonstrated that the LTT increased the antioxidative stress marker, Thiol, and, moreover, the antioxidant enzyme, GPx, and serum VEGF tended to increase. Furthermore, the marker of oxidative DNA damage, urine 8OHdG, significantly decreased after the LTT. These findings may indicate that the LTT decreased the oxidative stress contributing to the improvement in the NO bioavailability and upregulation of the VEGF, and could finally improve the endothelial function. A recent clinical study showed that an impaired FMD was a proven independent strong predictor of an adverse outcome and poor prognosis in patients with CHF (27). Thus, the LTT may improve the clinical outcome and prognosis in patients with CHF.

**LTT and vagal modulation**

In this study, we considered several possible mechanisms for the decrease in the HR (p=0.52) and systolic arterial pressure, but not significant change. One was the reduction in the venous return to the right atrium (RA). It is well known that an increase in the venous return to the heart causes an increase in the HR and cardiac output as the result of a stretched RA causing increased sinus node activity and a Bainbridge reflex (31). Further, the reduction in the venous return may cause a reduction in those activities resulting in a decrease in the HR and cardiac output, and ultimately the systemic arterial pressure, if decreased, would not be adequate to activate the sympathetic nerves to cancel those changes. Another possible mechanism is the activation of the vagal nerve. Despite being statistically insignificant, the LTT tended to decrease the LF/HF ratio. This indicated that the LTT may cause vagal nerve activation. There have been reports on somato-autonomic reflexes in which the effects of acupuncture on the lower extremities were described to cause a decrease in the HR (32). Local heat therapy might cause some similar effects as acupuncture in the same place. Further investigation will be necessary.

In addition to the direct effect of the LTT, there may be indirect effects of the LTT. Higashi et al. revealed that thermal therapy attenuated psychological stress (22). We think this may lead to parasympathetic activation, which may explain our findings. Activation of the vagal nerves is good for patients with CHF. Vagal nerve stimulation markedly improved the long-term survival of CHF rats through the prevention of pumping failure and cardiac remodeling (33). Further, it has been reported that vagal nerve activation-induced vasodilation is mediated by NO (34), and the LTT may benefit patients with CHF via vagal nerve activation which may lead to an improvement in the endothelial function and prevent the development of CHF.

**Comparison LTT and STT**

STT, and the rise in the core body temperature was 0.4 degrees on average, whereas STT caused about 1 degree rise in the core body temperature. However, improvement of %FMD was almost the same level (from 4% to 6%) (5). These results indicate that the elevation of body core tem-
perature by 0.4°C may be sufficient to improve the impaired endothelial function, which is an independent strong predictor of an adverse outcome and poor prognosis in patients with CHF (27). In view of these findings, LTT may be in no way inferior to STT.

Clinical implications

All patients completed this study without any LTT-associated adverse effects including worsened clinical symptoms, skin burns, hypotension, dehydration, or arrhythmias. The acute improvement in the FMD with LTT was similar to that of STT as previously described (6). Moreover, since the LTT does not require a dedicated spacious facility or any trained personnel, the LTT may easily and repeatedly be performed at a low cost anytime or anywhere, and would be applicable for any patient with CHF such as those that are bedridden.

Limitations of this study

The limitation of this study is the assessment of a relatively small number of patients and with many different causes of heart failure. In the present study, we evaluated only the acute effects, not long term effects, of the LTT, and performed the LTT in patients with mild to moderate CHF who were in NYHA functional class II or III (mean NYHA class = 2.8±0.6), and in a stable clinical condition for at least 1 month before the study entry. Whether our results can safely be extrapolated to patients with severe CHF and a greatly reduced LVEF should be determined in further studies. A recent case report showed that there was a similar beneficial effect of appendicular thermal therapy in patients with a more severe form of heart failure (22), further supporting our hypothesis.

Conclusion

LTT acutely improves the hemodynamics, vascular endothelial function, and oxidative stress in patients with CHF. LTT may be an effective, safe and attractive therapeutic strategy for patients with CHF. Supporting data from large clinical trials, however, are needed before such recommendations can be made. We plan to examine whether additional long-term LTT further decreases the oxidative stress, activates the vagal nerves, and improves the endothelial function and hemodynamic factors contributing to an improvement in the clinical status and prognosis of patients with CHF.

The authors state that they have no Conflict of Interest (COI).

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