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CORRESPONDENCE

Research Correspondence

Waon Therapy Improves Peripheral Arterial Disease

To the Editor: We developed a form of thermal therapy, namely "Waon therapy" (soothing warm therapy) (1), which differs from the traditional sauna, and demonstrated that the repeated use of a dry sauna at 60°C improves hemodynamics and ameliorates symptoms and vascular function in patients with chronic heart failure (2,3). Nitric oxide (NO), constitutively produced by endothelial nitric oxide synthase (eNOS), is a mediator of angiogenesis. Recently, we reported that repeated Waon therapy increases eNOS protein expression, blood flow, and capillary density in a mouse model of hind limb ischemia (4). Furthermore, Waon therapy does not increase blood flow and capillary density in eNOS-deficient mice, and we conclude that eNOS is a critical regulator of angiogenesis by Waon therapy.

Peripheral arterial disease (PAD) is a major cause of acute and chronic illness, associated with decrements in functional capacity and quality of life. We conducted this study to evaluate the beneficial effect of repeated Waon therapy using infrared-ray dry sauna on patients with PAD.

Patients were qualified for Waon therapy if they had chronic limb ischemia, including claudication, rest pain, and/or nonhealing ischemic ulcers present for a minimum of 4 weeks without evidence of improvement in spite of conventional therapies and were not candidates for surgical or nonsurgical revascularization. Requisite hemodynamic deficits included a resting ankle-brachial pressure index (ABI) <0.9 in the affected limb on 2 consecutive examinations performed at least 1 week apart. We enrolled 20 patients with PAD, including 15 patients with bilateral limb ischemia and 5 patients with unilateral limb ischemia.

The patients were placed in a far infrared-ray dry sauna, in which the temperature was evenly maintained at 60°C for 15 min, and then were kept on a bed outside the sauna for additional 30 min with sufficient warmth provided by blankets (2). They were weighed before and after Waon therapy, and oral hydration with water was used to compensate for weight loss. This Waon therapy was performed once a day for 5 days per week for a period of 10 weeks. Data were compared using paired *t* tests.

All patients enrolled in the trial completed the study without any adverse events. The demographic and clinical data of patients treated with 10-week Waon therapy are summarized in Table 1. Therapeutic benefit was demonstrated by regression of rest pain in all patients. Ischemic ulcers healed in all of the 7 limbs, resulting in successful limb salvage.

Leg pain was scored by a visual analog scale, using a marked 10-cm line extending from "no pain: 0" to "severe pain: 10." The pain score significantly decreased after 10 weeks of Waon therapy (Fig. 1A). Exercise performance, evaluated by the 6-min walking distance, improved in all 18 patients after 10 weeks of Waon therapy (Fig. 1B). We measured the ABI in 31 limbs, and the mean ABI significantly increased after Waon therapy (Fig. 1C). Serial assessment of leg blood flow was performed with laser Doppler imaging. It showed that blood flow increased after 10 weeks (Fig. 1D). Digital subtraction angiography was performed to evaluate new collateral vessel formation in 20 legs (13 patients), which showed a dramatic increase in the visible collateral vessels in 12 ischemic legs after 10 weeks of Waon therapy.

In summary, we have shown that repeated Waon therapy is safe for patients with severe PAD and potentially effective as evidenced by a substantial decrease in the pain score, increases in ABI and blood flow assessed by laser Doppler perfusion imaging, and by formation of new collateral vessels on angiography. In addition, ischemic ulcers present in 7 limbs healed or improved markedly. Given the poor prognosis of patients with chronic critical limb ischemia in whom the possibility of spontaneous improvement is remote, the outcome in this study is encouraging.

We reported that angiogenesis was induced via eNOS using Waon therapy in mice with hind limb ischemia (4). Nitric oxide is a mediator of angiogenesis and plays a key role in angiogenesis induced by Waon therapy. Repeated Waon therapy increases cardiac output, shear stress of the vessel wall, and ultimately eNOS expression.

Aicher et al. (5) reported that the impaired neovascularization in mice lacking eNOS is related to a defect in progenitor cell mobilization, and eNOS is essential for mobilization of stem and progenitor cells. We believe that our Waon therapy increases the number of circulating endothelial progenitor cells via partially NO-dependent. This may contribute to angiogenesis in patients with PAD, who are characterized by a reduced systemic NO bioactivity.

Exercise also increases circulating endothelial progenitor cells, and supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. The advantage of Waon therapy compared with exercise therapy for PAD is that we can successfully perform Waon therapy in patients who cannot exercise. Combinations of Waon therapy and exercise training might be useful for patients with PAD. Cellular and molecular therapeutic modalities for PAD have shown early efficacy. Therefore, we should analyze the synergistic effect of Waon therapy and gene transfer or therapeutic stem cell therapy.

We recently described one of the impressive patients (Patient #13 in Table 1) (6). His large skin ulcer healed completely after 15 weeks of Waon therapy, and limb amputation was avoided. In addition, 10 of 20 patients in this study were followed at our outpatient clinic and they continued Waon therapy at least twice per week. In the follow-up period ranging from 6 months to 3 years, none of them showed the worsening symptoms of PAD. Therefore, to maintain the effect of Waon therapy, we believe that treatment should be continued at least twice per week after discharge.

The limitation of this study is the lack of a control group. In the absence of a control group, the treatment effect cannot be estimated, confounding standard care variables are not defined, and enrollment bias could lead to comparable rates of clinical improve-

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Table 1 Clinical Data Before and After Waon Therapy

Clinical History and Findings Before Waon Therapy							Outcome After Waon Therapy	
Patient #	Gender	Age (yrs)	Smoking	DM	Previous Surgery	Signs/Symptoms	Limb Status	ABI
1	F	79	−	−	None	Leg ulcer	Leg ulcer completely healed	Rt 0.76→0.86/Lt 0.70→0.82
2	M	63	+	+	None	Leg ulcer Toe ulcer (digits I, II)	Leg ulcer completely healed Toe ulcer improved	Rt Im/Lt Im
3	M	70	−	+	Below knee amputation F-F bypass	Rest pain	Rest pain resolved	Rt Im/Lt 0.60→0.74
4	M	75	+	−	None	Intermittent claudication	Walking distance increased	Rt 0.68→0.79/Lt 0.82→0.95
5	F	82	−	+	None	Intermittent claudication	Walking distance increased	Rt 0.56→0.64/Lt 0.74→0.76
6	F	72	−	−	None	Rest pain	Rest pain resolved	Rt 0.76→0.70/Lt 1.05→1.03
7	M	80	−	−	None	Intermittent claudication	Walking distance increased	Rt 0.30→0.40/Lt 0.82→0.84
8	F	88	−	+	None	Rest pain	Rest pain resolved	Rt 0.54→0.60/Lt 0.75→0.60
9	M	77	+	+	None	Toe ulcer (digit II)	Toe ulcer improved	Rt 0.64→0.72/Lt 0.98→1.02
10	M	75	+	−	None	Intermittent claudication	Walking distance increased	Rt 0.55→0.61/Lt 0.50→0.56
11	M	76	+	+	None	Intermittent claudication	Walking distance increased	Rt 0.65→0.74/Lt 0.38→0.54
12	M	80	+	−	None	Toe ulcer (digit I)	Toe ulcer improved	Rt Im/Lt 0.30→0.55
13	M	64	+	+	Toe amputation F-P bypass, P-T bypass	Toe ulcer	Toe ulcer completely healed	Rt Im→0.37/Lt 0.81→0.85
14	M	66	+	−	Toe amputation F-P bypass	Toe ulcer	Toe ulcer completely healed	Rt 0.74→0.74/Lt 0.79→0.79
15	M	73	+	+	None	Intermittent claudication	Walking distance increased	Rt 0.63→0.81/Lt 0.64→0.82
16	M	66	+	−	Toe amputation F-P bypass	Rest pain	Rest pain resolved	Rt Im/Lt 1.01→1.00
17	M	73	+	+	None	Intermittent claudication	Walking distance increased	Rt 0.44→0.44/Lt 0.45→0.46
18	F	79	−	+	None	Intermittent claudication	Walking distance increased	Rt 0.54→0.65/Lt 0.51→0.52
19	M	81	+	+	None	Intermittent claudication	Walking distance increased	Rt 0.48→0.49/Lt 0.49→0.50
20	M	68	+	+	None	Intermittent claudication	Walking distance increased	Rt 0.51→0.55/Lt 1.10→1.10

ABI = ankle brachial pressure index; DM = diabetes mellitus; F-F = femoral-femoral artery; F-P = femoral-popliteal artery; Im = impossible to measure; Lt = left; P-T = popliteal-tibial artery; Rt = right.

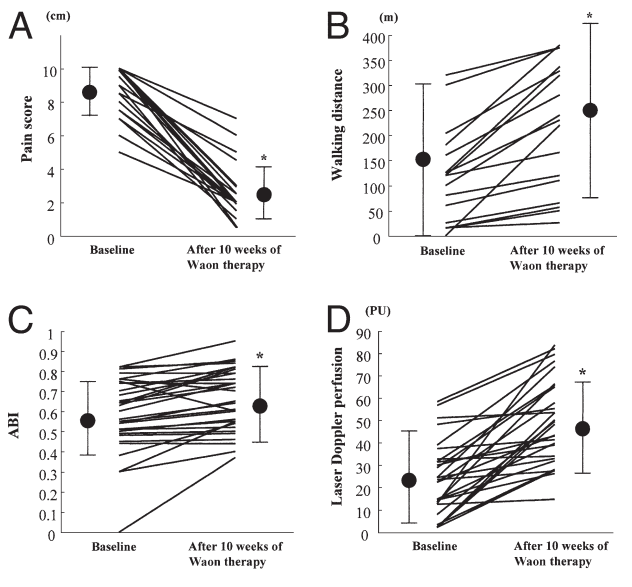

Figure 1 Improvement in Pain, Walking, ABI, and Blood Flow After 10 Weeks of Waon Therapy

(A) Pain score evaluated by a visual analog scale (10 = severe pain, 0 = no pain) (n = 20); **(B)** 6-min walking distance (n = 18); **(C)** ankle-brachial pressure index (ABI) (n = 31); and **(D)** laser Doppler perfusion imaging (n = 28). *p < 0.01.

ment. Randomized and controlled trials with larger numbers of patients with PAD will help to determine the efficacy of Waon therapy.

In conclusion, we demonstrated that Waon therapy improved symptoms, status, and blood flow in patients with PAD. Our Waon therapy method may therefore be a novel innovative therapy for patients with PAD.

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Letters to the Editor

Complex Roles of Endothelial Shear Stress in Vascular Remodeling Response

With great interest I read the review article by Chatzizisis et al. (1) regarding endothelial shear stress (ESS), coronary atherosclerosis, and vascular remodeling. The authors stated in the text, "Recent observations, however, indicate that low ESS leads to excessive expansive remodeling . . ." from their diabetic hyperlipidemic swine model. However, in their previous human study (2), they demonstrated that constrictive remodeling occurred more frequently (44%) than expansive remodeling (22%) in subsegments with low ESS, whereas expansive remodeling occurred more frequently (26.3%) than constrictive remodeling (5.3%) in subsegments with moderate/higher ESS. These results suggest complex roles of ESS in the vascular remodeling response, depending on concomitant conditions including atherosclerotic stage, in addition to differences in biology between experimental models and clinical studies (3,4). Further clinical studies are warranted to determine the role of ESS in vascular remodeling in humans.

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Reply

Dr. Kaneda appropriately draws attention to the complexity of vascular remodeling. The magnitude of low endothelial shear stress (ESS), as well as changes in ESS and the rate of change in ESS, all contribute to the pathobiology of atherosclerosis (1,2). In our human pilot study, we observed expansive remodeling in areas of initially low or high ESS. It is therefore likely that expansive remodeling occurs through different mechanisms in different local environments and under different flow regimes (3).

Low ESS enhances lipid accumulation and local inflammation. The enzymatic degradation of the underlying internal elastic lamina and media that follow ultimately lead to expansive remodeling (1). Whether the expansive remodeling response becomes excessive or compensatory is likely dependent on the magnitude of low ESS (1). Very low ESS induces an intense inflammatory response that leads to excessive lumen and wall expansion (excessive expansive remodeling) (1). These wall changes further reduce local ESS, establishing a cascade of inflammation and excessive expansive remodeling, which can transform a stable plaque into a thin cap fibroatheroma. In contrast, in areas with limited reductions in ESS, local inflammation is modest, and the cellular reaction might strengthen the plaque and lead to compensatory expansive remodeling (1). The changes in the vessel wall and the minimal narrowing of the lumen might restore ESS to more physiologic levels and thereby promote plaque quiescence.

High ESS might also lead to expansive remodeling, but through a different mechanism. Reactive dilation of the plaque-free wall with normal flow-responsive endothelium in the area of an eccentric plaque can normalize the local ESS environment (4).

In our human pilot study (3), we observed that areas with low baseline ESS can develop constrictive remodeling at follow-up. Although the pathobiologic mechanisms responsible for constrictive remodeling are less clear than those of expansive remodeling, constrictive remodeling in our patients may have been related to subclinical plaque microrupture and subsequent healing (5). Alternatively, a fibroproliferative smooth-muscle cell phenotype may have been consistently operative throughout the natural history course of that plaque.

We agree that it is critical to understand these vascular behavior patterns in more detail because the ultimate clinical manifestations of coronary disease depend on the morphologic evolution and flow remodeling of the atherosclerotic plaque (1). Although clinical studies are essential to the identification of atherosclerotic patterns, animal models enable specific delineation of the dynamic and

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