

Effect of Stress-free Therapy on Cerebral Blood Flow: Comparisons among patients with metabolic cardiovascular disease, healthy subjects and placebo-treated subjects

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Background and aims: We have developed a Stress-free Therapy[®] device wherein “Pinpoint Plantar Long-wavelength Infrared Light Irradiation (PP-LILI)” increases peripheral-deep body temperature and blood flow volume and stabilizes blood pressure as well as significantly reduces stress hormones such as adrenocorticotrophic hormone and cortisol without using drugs. Moreover, we have found this therapy to significantly improve blood glucose and insulin resistance in patients with type 2 diabetes. Based on this background of clinical efficacy, we validated changes in cerebral blood flow in patients with metabolic cardiovascular disease and examined the efficacy of Stress-free Therapy[®] on cerebral blood flow as compared to that in healthy control subjects and placebo-treated patients.

Results: The change in cerebral blood flow volume during 15-minute PP-LILI was 5.1 ± 1.8 mL/min in patients with metabolic cardiovascular disease, showing a significant increase ($P < 0.05$) of 3.1 mL/min as compared with the mean blood flow value after resting for 15 minutes.

Conclusions: Our results suggested Stress-free Therapy[®] to significantly increase cerebral blood flow, possibly leading to the prevention of metabolic cardiovascular disease.

Introduction

We have developed a novel Stress-free Therapy[®] wherein Pinpoint Plantar Long-wavelength Infrared Light Irradiation (PP-LILI) increases peripheral-deep body temperature and blood flow volume and stabilizes blood pressure as well as significantly reduces stress hormones such as adrenocorticotrophic hormone (ACTH) and cortisol without using drugs. Furthermore, we demonstrated that this therapeutic method significantly improves blood glucose and insulin resistance in patients with type 2 diabetes.^{1, 2)} Based on these initial results, we determined the presence or absence

and the degree of the preventive effect of Stress-free Therapy[®] on diabetes, which is considered to be present in at least 10% of the Japanese population. As there are no subjective symptoms in the early stage of diabetes, which is detected based on high blood glucose levels, patients do not generally visit a hospital to receive proper treatments. When diabetes is left untreated, it results in decreased cerebral blood flow, inducing Alzheimer's disease, and moreover, serious complications such as stroke, myocardial infarction, retinopathy, nephropathy, and neuropathy.³⁻⁶⁾ Herein, we comparatively examined the effect of Stress-free Therapy[®] on cerebral blood flow volume in patients with metabolic cardiovascular disease such as diabetes, healthy volunteers, and placebo-treated patients.

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Methods

The subjects were 20 patients with metabolic cardiovascular disease (9 men, 11 women; mean age, 62.5 ± 11.5 years), 10 healthy volunteers (6 men, 4 women; mean age, 28.8 ± 7.3 years), and 10 placebo-treated patients (5 men, 5 women; mean age, 40.8 ± 11.2 years; undergoing only placement of a probe without irradiation). The subjects were randomly selected for comparison. With regard to irradiation conditions, PP-LILI was delivered after patients had rested in the supine position for 15 minutes. The irradiation point was the intersection of the centers of the heads of the first and second metatarsal bones of the sole and a vertical line drawn from the medial malleolus using the Stress-free Therapy® device (Controlled medical device certificate No. 224AFBZX00075000; probe diameter 20 mm, far-infrared wavelength 9000 to 12000 nm, output 30 mW). Blood flow volumes before and after irradiation were measured and changes were then determined (**Fig. 1**). To determine cerebral blood flow changes, we used laser Doppler flowmetry (Advance, ALF21) to quantitatively analyze blood flows in the facial artery (mL/min) after patients had rested for 15 minutes, during 15-minute treatment with PP-LILI, and for 15 minutes after treatment (**Fig. 2**).

Ethical considerations

We explained to the subjects verbally and in writing the objectives and safety of the study. We also provided assurance that “subjects will not be treated disadvantageously by withdrawing their consent to cooperate in the study after the study started” and “information obtained in this study will not be used other than in research presentation (information identifying names, etc. will not be disclosed)” and obtained their



Figure 1: Stress-free Therapy® Device (Left) and Stimulation Point (Right)

consent. The study was conducted after obtaining approval from the ethics review board of Ryotokuji University (approval No. 2304).

Statistical analysis

ANOVA was applied and multiple comparisons were performed using Tukey - Scheffé tests, with a significance level of $p < 0.05$.

Results

The mean blood flow volume in the facial artery (**Fig. 3**) before PP-LILI (value after 15-minute rest) was 2.0 ± 0.6 mL/min in patients with metabolic cardiovascular disease, 2.7 ± 1.6 mL/min in healthy volunteers, and 2.6 ± 1.6 mL/min in placebo-treated subjects, showing low blood flow in patients with metabolic cardiovascular disease.

The change in cerebral blood flow volume during 15-minute PP-LILI using the Stress-free Therapy® device was 5.1 ± 1.8 mL/min in patients with metabolic cardiovascular disease, showing a significant increase ($P < 0.05$) of 3.1 mL/min as compared with the mean blood flow value after resting for 15 minutes. The blood flow volume tended to increase in healthy controls (4.7 ± 2.8 mL/min) and the placebo-treated subjects (3.4 ± 2.8 mL/min), but the changes did not reach statistical significance. Furthermore, with regard to changes in cerebral blood flow volume during 15 minutes after PP-LILI, a significant increase ($P < 0.05$) was

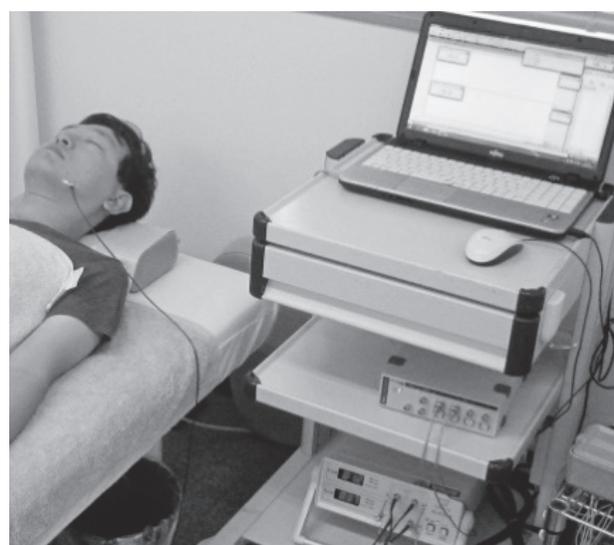


Figure 2: Measurement of Cerebral Blood Flow (Facial Artery)

observed only in patients with metabolic cardiovascular disease (5.2 ± 2.0 mL/min). Neither healthy volunteers (5.2 ± 2.8 mL/min) nor placebo-treated subjects (3.1 ± 3.0 mL/min) showed a significant increase in cerebral blood flow. In patients with metabolic cardiovascular disease, cerebral blood flow volume was lowest at rest. However, PP-LILI significantly increased the blood flow volume as compared with the values in other subjects (healthy volunteers and placebo-treated patients). Meanwhile, blood flow increased by 2.5 mL/min, at a maximum, in healthy volunteers as compared with blood flow at rest, not a significant difference. Furthermore, as placebo-treated subjects showed only a minimal increase of no more than 0.8 mL/min as compared with cerebral blood flow at rest, the absence of any meaningful placebo effect was confirmed.

Discussion

In mouse models of Alzheimer's disease with concurrent diabetes, β -amyloid protein deposition reportedly occurs in cerebral blood vessels, resulting in stenosis of cerebral blood vessel walls and/or a markedly increased inflammatory response.³⁻⁶ It has been pointed out that these changes decrease cerebral blood flow by impeding normal cerebrovascular responsiveness, thereby possibly exacerbating ischemic brain disorders and cognitive function impairment.⁷ Our pre-

sent results also confirmed cerebral blood flow to be decreased in patients with metabolic cardiovascular diseases such as diabetes as compared with healthy volunteers. These results clearly indicate cerebrovascular metabolism, including metabolic activities in cranial tissues, to be more adversely affected than expected in patients with metabolic cardiovascular diseases such as diabetes, suggesting that early identification and early treatment before the onset of diabetes-induced ischemic brain disorders and cognitive function impairment are very important. However, as diabetes presents have few subjective symptoms, the patients do not recognize its onset, allowing vascular damage and complications to develop prior to recognition of the need for intervention. In this study, a noninvasive and easy-to-use Stress-free[®] Therapy device, i.e., our novel PP-LILI, significantly improved the reduced cerebral blood flow observed in patients with metabolic cardiovascular disease ($p < 0.05$). Furthermore, we showed in our earlier studies that PP-LILI is effective for improving insulin resistance and decreasing stress hormones in patients with type 2 diabetes.^{1,2} We also have reported that behavioral and psychological symptoms of dementia (BPSD) were ameliorated as the cerebral blood flow in patients with early-stage dementia improved.⁸ Taken together, the results of these studies suggest that PP-LILI is likely to be an effective therapy for preventing both the onset and the recurrence of metabolic cardiovascular diseases. Meanwhile, various stress responses in the body are known to stimulate the sympathetic nervous system and regulate the functions of the parasympathetic nervous system, thereby reducing the peripheral blood flow volume including the head.⁹ Bathing and foot baths are recommended for coldness of the extremities resulting from such stress; heating the entire body by bathing, etc. promotes activation of biological defense mechanisms such as autonomic nerve responses and immunity, with amelioration of disease states being anticipated. However, when the entire body is heated, symptoms such as transient dehydration, flushing, and dizziness can be induced due to rapid increases in body temperature and fluid pressure, raising concerns about the onset of cardiovascular and cerebrovascular events resulting from excessively increased blood flow. However, these adverse events are considered to be preventable with the application of PP-LILI, employing the Stress-free Therapy[®] device, to the soles of the feet, which increases blood flow without burdening the cardiovascular system. Moreover, blood flow was slightly increased, by 2.5 mL/min as compared with the value at rest, in healthy volunteers, indicating that

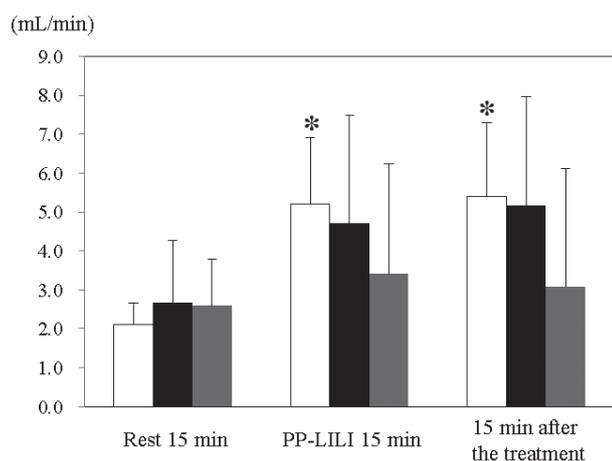


Figure 3: Changes in Cerebral Blood Flow (Facial Artery)
 □ Patients with metabolic cardiovascular disease;
 ■ Healthy volunteers,
 ▒ Placebo-treated subjects; mean \pm SD, after resting for 15 min. vs. $P < 0.05^*$

comfortably applying PP-LILI to the soles of the feet exerted a sedating effect on the sympathetic nerves and thereby mildly improved systemic hemodynamics, without imposing an excessive burden on the cardiovascular system. Furthermore, some reports have suggested the involvement of vascular endothelial growth factor (VEGF) genes in the onset of diabetes and the complications.¹⁰⁻¹²⁾ We are now actively examining the association between VEGF and cerebral blood flow by focusing on hemodynamics and Alzheimer's disease attributable to diabetes, and the associated cerebral dysfunction.

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Conclusions

We have comparatively examined the efficacy of our Stress-free Therapy[®] device on cerebral blood flow in patients with metabolic cardiovascular disease, healthy control subjects and placebo-treated subjects. The results obtained in this study suggest that this novel device significantly increases cerebral blood flow, thereby possibly leading to the prevention of metabolic cardiovascular disease.