

Biological effect of far-infrared therapy on increasing skin microcirculation in rats

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Background/purpose: Insufficient microcirculation of skin leads to acute and chronic tissue ischemia in cases of trauma, reconstructive surgery, diabetes mellitus and peripheral arterial occlusive disease. The autonomic nervous system and nitric oxide (NO) play important roles in maintaining blood perfusion of the skin. Far-infrared (FIR) therapy provides low energy of light emitted from an artificial radiator and has been used to treat many vascular-related disorders. Nevertheless, the mechanisms through which FIR works remain unclear. The present study aims to test the hypothesis that the effect of FIR is through increasing skin microcirculation by a mechanism other than its thermal effect.

Methods: Sixty rats were used in the present study. A WS™ TY301 FIR emitter was placed 20 cm above the rats. Skin temperature and blood flow were continuously measured by a K-type thermocouple. Under laboratory control, the abdominal skin temperature steadily increased from 38–39 °C, and was kept at constant temperature. Skin microcirculation was measured with a continuous laser Doppler flowmeter.

Infrared radiation is an invisible electromagnetic wave adjacent to the visible light region on the wave spectrum in nature. It has a longer wavelength than visible light. Infrared radiation transfers energy, in the form of heat, to surrounding tissues and can be perceived as heat by thermoreceptors in the surrounding skin (1). Infrared radiation is subdivided into three categories: near-infrared radiation (0.8–1.5 μm), middle infrared radiation (1.5–5.6 μm) and far-infrared (FIR) radiation (5.6–1000 μm). FIR therapy uses low-energy of light emitted from an artificial radiator. FIR has been used to treat many vascular-related disorders

Results: There was no significant change of skin blood flow during FIR treatment. Skin blood flow increased significantly soon after the removal of the FIR emitter. The stimulating effect on skin blood flow was more significant in the rats treated with FIR for 45 min and could be sustained as long as 60 min. These findings suggested a non-thermic biological effect of FIR on skin microcirculation. The promotive effect of FIR on increasing skin blood flow was not influenced by pretreatment of APP (atropine, propranolol and phen-tolamine), but was suppressed by pretreatment with N^G-nitro-L-arginine methyl ester (an endothelial nitric oxide synthase inhibitor).

Conclusion: In conclusion, FIR therapy exerts a NO-related biological effect to increase skin microcirculation in rats. This might bring into perspective the clinical application of FIR to treat ischemic disease by augmenting L-arginine/NO pathway.

Key words: far-infrared; FIR; nitric oxide; NO; skin microcirculation.

(2, 3). Although the technology of FIR irradiation has been widely applied in health promotion (4–6) and food preservation (7, 8), the exact mechanisms of the hyperthermic effects and biological activities of FIR irradiation are still poorly understood.

Insufficient microcirculation of skin leads to tissue ischemia, loss of function in peripheral tissues, and, eventually, tissue necrosis. Clinical applications include acute and chronic tissue ischemia observed in major trauma, reconstructive surgery, diabetes mellitus and peripheral arterial occlusive disease. The autonomic nervous system (9–11) and nitric oxide

(12–16) have been reported to have important roles in maintaining blood perfusion of skin. To increase the recovery rate of circulatory insufficiency, physicians have attempted adjunctive therapies in addition to the conventional treatments. The adjunctive therapies included hyperbaric oxygenation (17–22), low-energy laser therapy (23–25), local somatothermal stimulation (26, 27), Chinese herb therapy (28, 29), acupuncture (30) and FIR therapy (31, 32).

The aims of this study were to test the hypothesis that FIR therapy is effective in increasing skin microcirculation and to elucidate the mechanisms of how FIR works.

Materials and methods

Animal

Sixty male Sprague–Dawley rats weighing between 250 and 300 g were obtained from the animal center of the National Science Council, Taiwan, China. The rats were fed with standard diet and water *ad libitum* and treated under the regulations of the ‘Principles of laboratory animal care’ (NIH publication No. 86-23, revised, 1985). The study was approved by the committee of experimental animals of National Yang-Ming University.

FIR therapy

A WS™ TY301 FIR emitter (Far IR Medical Technology Co., Ltd., Taipei, Taiwan) was used for this study (Fig. 1a). The wavelength of the light generated from the electrified ceramic plates was in the range between 5 and 12 μm with a peak at 8.2 μm (Fig. 1b). To avoid the interference from environment, the experimental field was surrounded by a wooden hedge. The top radiator was placed 20 cm above the rats in order to raise the abdominal skin temperature steadily. The TY301 FIR radiator used in this experiment could be adjusted (manually or automatically) to control the surface temperature between 38 and 39 °C. Under laboratory control, the surface temperature was raised to a plateau between 38 and 39 °C. The room temperature was approximately 18–20 °C.

Animal model for microcirculation-impaired skin flap

The microcirculation-impaired injury of a skin flap in a rat model was performed as described previously (33). In brief, male Sprague–Dawley rats were anesthetized with ketamine (100 mg/kg, intraperitoneally) and urethane (1000 mg/kg, intraperitoneally). The flap was raised, based on the left superficial epigastric artery and vein. The right superficial epigastric artery and vein were ligated. A permanent flap ischemia was induced by ligating the left superficial

epigastric vascular pedicle for 2 h (Devascularization-Flap group, $n = 6$). In another group of rats flap ischemia was induced by clamping the left superficial epigastric vascular pedicles for 1 h and then releasing the clamps (Ischemia-Flap group, $n = 6$). In the third group of rats flap ischemia was induced by clamping the left superficial epigastric vascular pedicles for 1 h and then releasing the clamps for another 1 h to induce reperfusion injury (Reperfusion-Flap group, $n = 6$). All skin flaps were sutured back with the placement of a non-absorbable mesh. The mesh was placed just beneath the skin flap to prevent spread of angiogenesis from the wound bed.

Measurement of skin temperature and blood flow

- (1) Applications for measuring skin temperature and skin blood flow: after anesthetizing the rats, skin between the midpoints of the subphrenic lines and inguinal lines (dotted lines in Fig. 1c) were shaved and equally irradiated by FIR. A K-type thermocouple was placed halfway along the upper abdominal midline (designated as T in Fig. 1c) and the skin temperature was recorded continuously. At the same time, skin blood flow was measured with a continuous laser Doppler flowmeter (LDF100A, BIOPAC Systems Inc.; wavelength = 780 ± 10 nm, Bandwidth = 10 Hz–22 kHz, response time = 100 ms). A miniature surface probe (TSD 143, BIOPAC Systems Inc., Goleta, CA, U.S.A.) was placed halfway along the lower abdominal midline (designated as D in Fig. 1c). The thermocouple was placed over different points of illuminated skin in rats ($n = 6$) to make sure that the skin was effectively equally irradiated by FIR. The skin temperature was recorded in degrees celcius (°C) and the skin blood flow was recorded in blood perfusion units (BPU).
- (2) Skin blood flow as a parameter of evaluating FIR effect: laser Doppler flowmeter was applied to flaps with circulatory impairment (established above). A group of normal rats ($n = 6$) served as control. All rats received 30 min of FIR therapy, followed by another 15 min of observation for post-FIR irradiation effects. Skin blood flow was continuously measured before, during and after FIR treatment.
- (3) Time effect of FIR therapy and post-FIR effect: rats were exposed to FIR for 30 min ($n = 6$), 45 min ($n = 6$) or 60 min ($n = 6$). Skin temperature and blood flow were continuously measured. The average BPU value of the last 6 min of FIR irradiation was designated as During-FIR. The

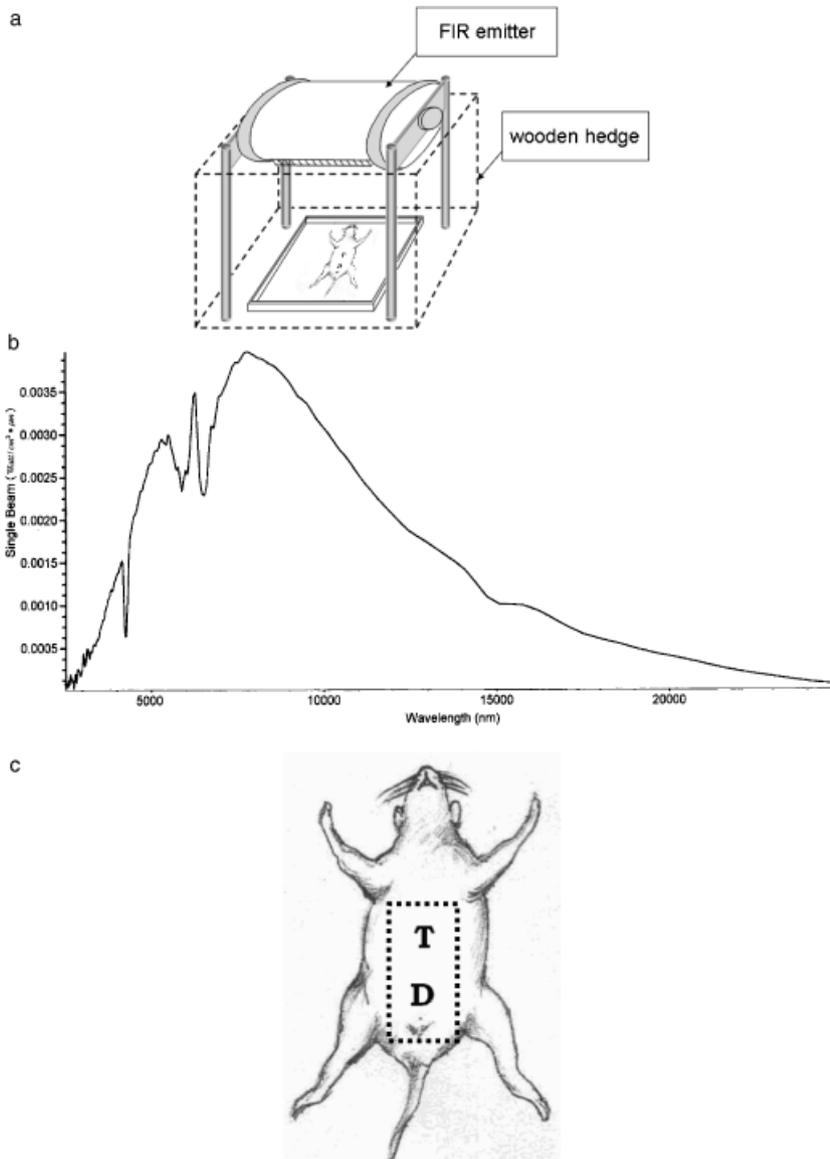


Fig. 1. Experimental setup for far-infrared (FIR) therapy. FIR therapy was achieved by a WS™ TY301 FIR emitter (a). The wavelength, tested by China National Infrared Products Quality Supervision and Testing Center, of the light generated from the electrified ceramic plates was in the range between 5 and 12 μm with a peak at 8.2 μm (b). Skins between mid-points of subphrenic lines and inguinal lines (dotted lines in c) were shaved and equally irradiated by FIR. A K-type thermocouple was placed over the half-way of upper abdominal midline (designated as T). Skin blood flow was measured with a continuous laser Doppler flowmeter by placing a miniature surface probe halfway along the lower abdominal midline (designated as D).

average BPU value 6 min before the start of FIR therapy served as the baseline. After giving 30, 45 or 60 min of FIR therapy, the FIR emitter was removed and the abdominal skin blood flow was continuously recorded. The average BPU value of the last 6 min of post-FIR observation was designated as post-FIR.

Drug administration

Atropine, propranolol and phentolamine (APP) was used to determine whether the promotive effect on skin microcirculation was through the autonomic nervous system. Nitric oxide (NO), regulated by endothelial nitric oxide synthase (eNOS), synthesized in vascular endothelial cells has been claimed to play an important role in the control of blood pressure. NOS activity can be inhibited by the stereospecific molecule, *N*^G-nitro-L-arginine methyl ester (L-NAME). Male

Sprague–Dawley rats were anesthetized with ketamine and urethane. As described previously (21), a femoral artery and a femoral vein were cannulated and maintained for monitoring and for intravenous administrations. Rats were randomly divided into two groups as follows: (1) APP group ($n = 6$): atropine sulfate (A0257, Sigma Co., MO, USA) 30 μg/kg, propranolol (P0884, Sigma Co) 2 μg/kg and phentolamine (P7547, Sigma Co.) 1.5 mg/kg; (2) L-NAME group ($n = 6$): L-NAME (N5751, Sigma Co.) 100 μg/kg/min.

Statistics

Data were presented as mean ± SEM. For statistical evaluation between groups, determined by using unpaired *t*-test, data with *P* value less than 0.05 were considered significant. All statistical analyses were performed with SigmaStat 2.0 (Aspire Software International, Leesburg, VA, USA).

Results

Measurement of blood flow in normal skins and microcirculation-impaired flaps

The laser Doppler flowmeter was applied underneath the normal skins and microcirculation-impaired flaps, and blood perfusion expressed as BPU before, during and after FIR therapy was recorded continuously. In the control group (normal rats), the baseline was higher with a significant increase in post-FIR skin blood flow (Fig. 2). The baseline values of skin blood flow in all microcirculation-impairment flaps decreased significantly (Fig. 2) and did not respond to FIR therapy (data not shown).

Time effect of FIR therapy: thermic effect

When the top FIR radiator was 20 cm above the rats, the abdominal skin temperature steadily increased to a plateau between 38 and 39 °C (Figs 3a, 4a, 5a). To study the time response on skin blood flow, male Sprague–Dawley rats were treated with FIR with different time courses, for durations of 30 min

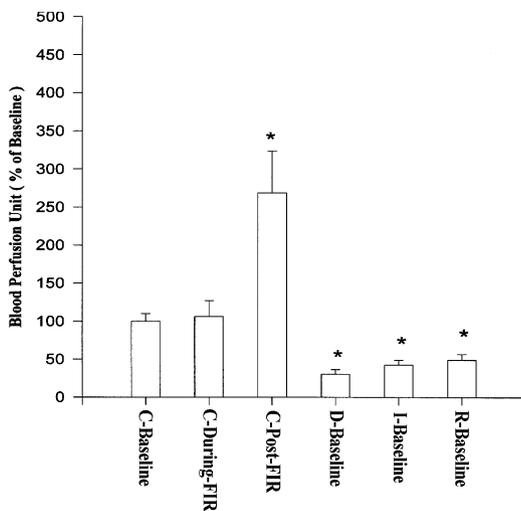


Fig. 2. Measuring blood flow in normal skins and microcirculation-impaired flaps. C, Control group. D, Devascularization-Flap group. I, Ischemia-Flap group; R, Reperfusion-Flap group. Baseline, average of 6–0 min before far-infrared (FIR) therapy. During FIR, average of 24–30 min of FIR therapy. Post-FIR, average of 9–15 min after FIR therapy. All rats received 30 min of FIR therapy, followed by another 15 min of observation for post-FIR effects. In the control group, the baseline was higher with a significant increase in post-FIR skin blood flow. The baseline values of skin blood flow in all microcirculation-impairment flaps decreased significantly and did not respond to FIR treatment (data were not shown). Data were presented as mean \pm SEM. * $P < 0.05$ compared with C-Baseline.

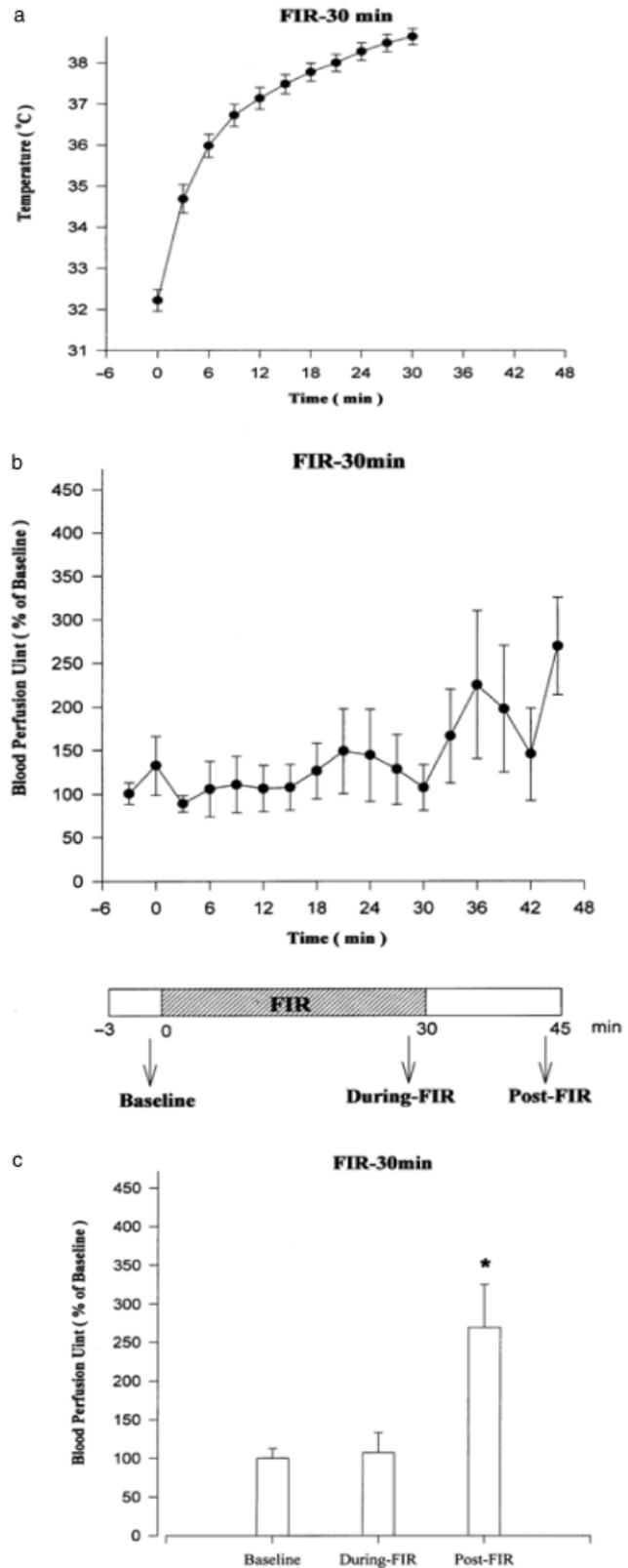
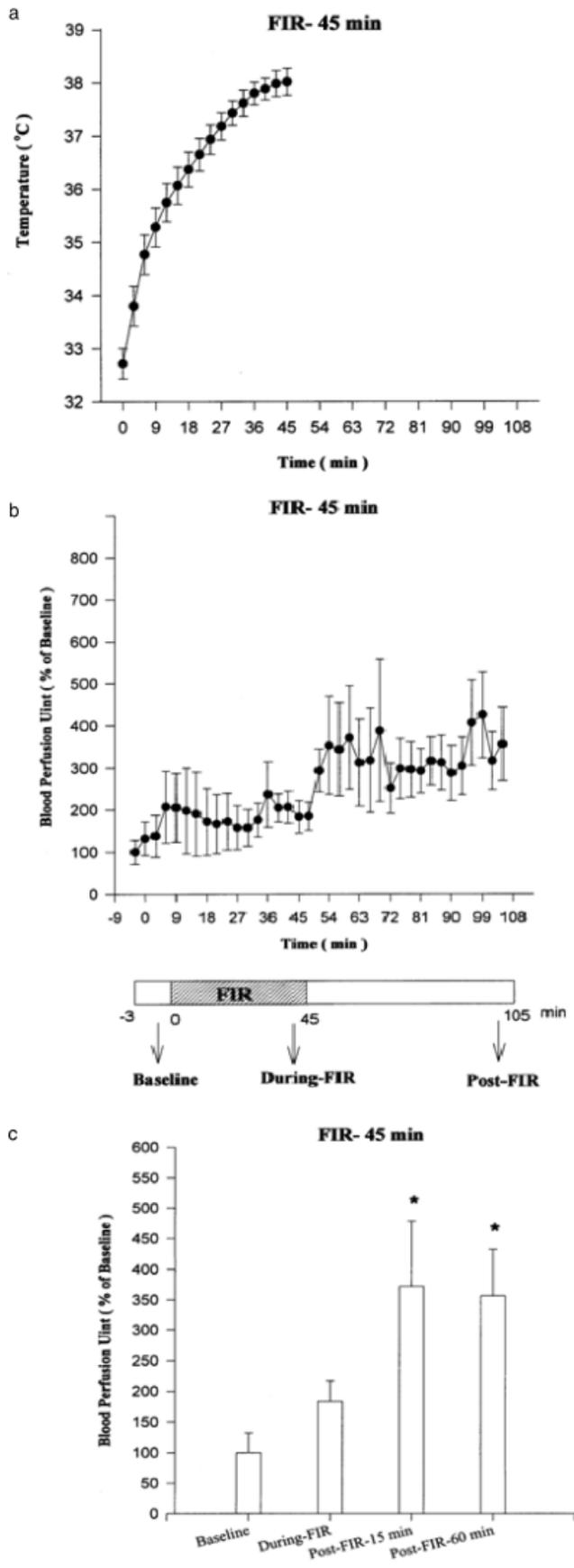


Fig. 3. (a) Effect of far-infrared (FIR) therapy (30 min) and post-FIR effect on skin blood flow. There was no significant change of skin blood flow during FIR treatment. Skin blood flow increased significantly after the removal of the FIR emitter (b, c). Data were presented as mean \pm SEM. * $P < 0.05$ compared to Baseline.



($n = 6$, Fig. 3b and c), 45 min ($n = 6$, Fig. 4b and c) or 60 min ($n = 6$, Fig. 5b and c). There was no significant change of skin blood flow during FIR treatment. The increase in skin temperature, resulted from direct exposure to FIR, did not relate to the change of skin blood flow.

Post-FIR effect: non-thermic biological effect

After being treated with FIR with different time courses, for durations of 30 min ($n = 6$, Fig. 3b and c), 45 min ($n = 6$, Fig. 4b and c) or 60 min ($n = 6$, Fig. 5b and c), the FIR emitter was removed and the skin blood flow was continuously recorded to evaluate the post-FIR response. Skin blood flow increased significantly soon after the removal of the FIR emitter in all groups. The stimulating effect of skin blood flow was more significant in the rats treated for 45 min with FIR radiation, and could be maintained as long as 60 min (Fig. 4b). These findings suggested a non-thermic biological effect of FIR radiation on skin blood flow.

Effect of APP on FIR-enhanced microcirculation

Rats ($n = 6$) were pretreated with APP 15 min before a 45-min course of FIR treatment. Skin temperature and blood flow were measured as previously mentioned (Fig. 6a–c). The character of blood flow enhancement was not eliminated by APP pretreatment, thus suggesting that the autonomic component contributed little to the non-thermal biological effect of FIR ray on rat skin.

Effect of L-NAME on FIR-enhanced microcirculation

Rats ($n = 6$) were treated with L-NAME 15 min before the 45-min course of FIR therapy. Skin temperature and blood flow were measured continuously (Fig. 7a, b and c). In comparison with Figs 4b,c, 6b,c, the curve of skin blood flow was dampened and it lost its tendency to elevate after FIR therapy. The results suggested that L-NAME pretreatment suppressed the stimulating effect of FIR radiation on skin blood flow in rats (Fig. 7b and c).

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Fig.4. (a) Effect of far-infrared (FIR) therapy (45 min) and post-FIR effect on skin blood flow. There was no significant change of skin blood flow during FIR treatment. Skin blood flow increased significantly after the removal of the FIR emitter (b, c). Data were presented as mean \pm SEM. * $P < 0.05$ compared with baseline.

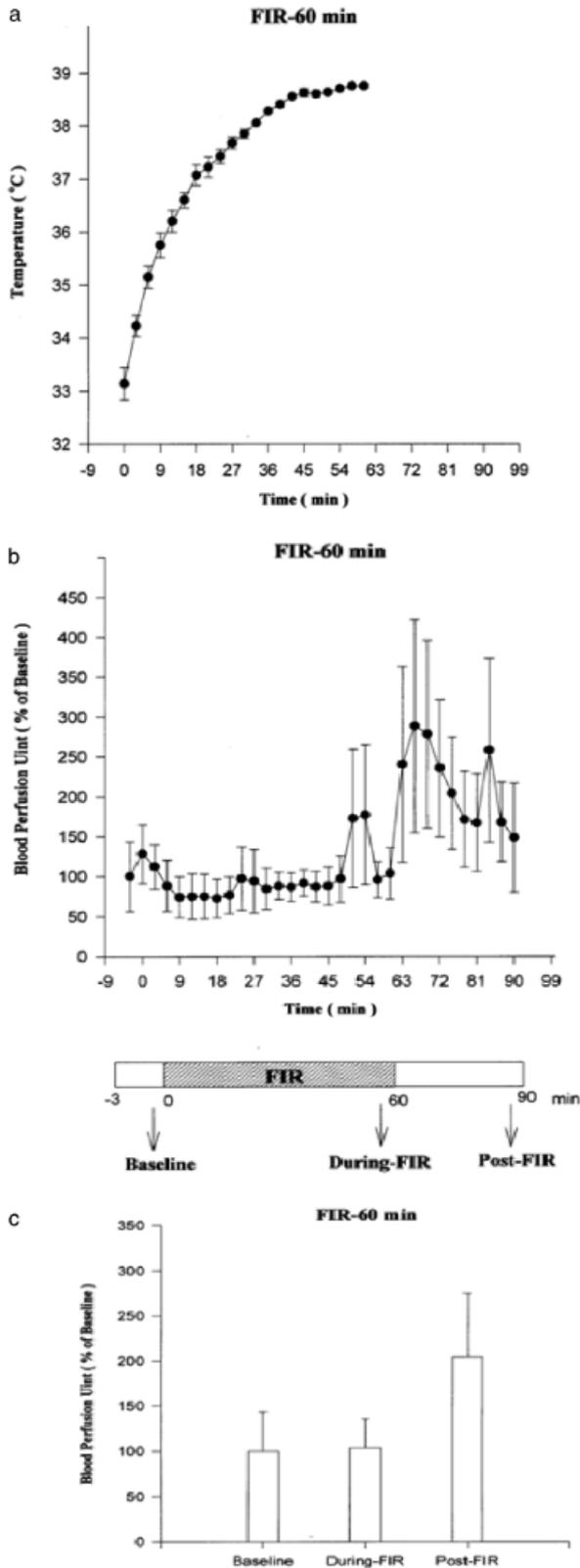


Fig. 5. (a) Effect of far-infrared (FIR) therapy (60 min) and post-FIR effect on skin blood flow. There was no significant change of skin blood flow during FIR treatment. There was a tendency of skin blood flow to increase after the removal of the FIR emitter (b, c).

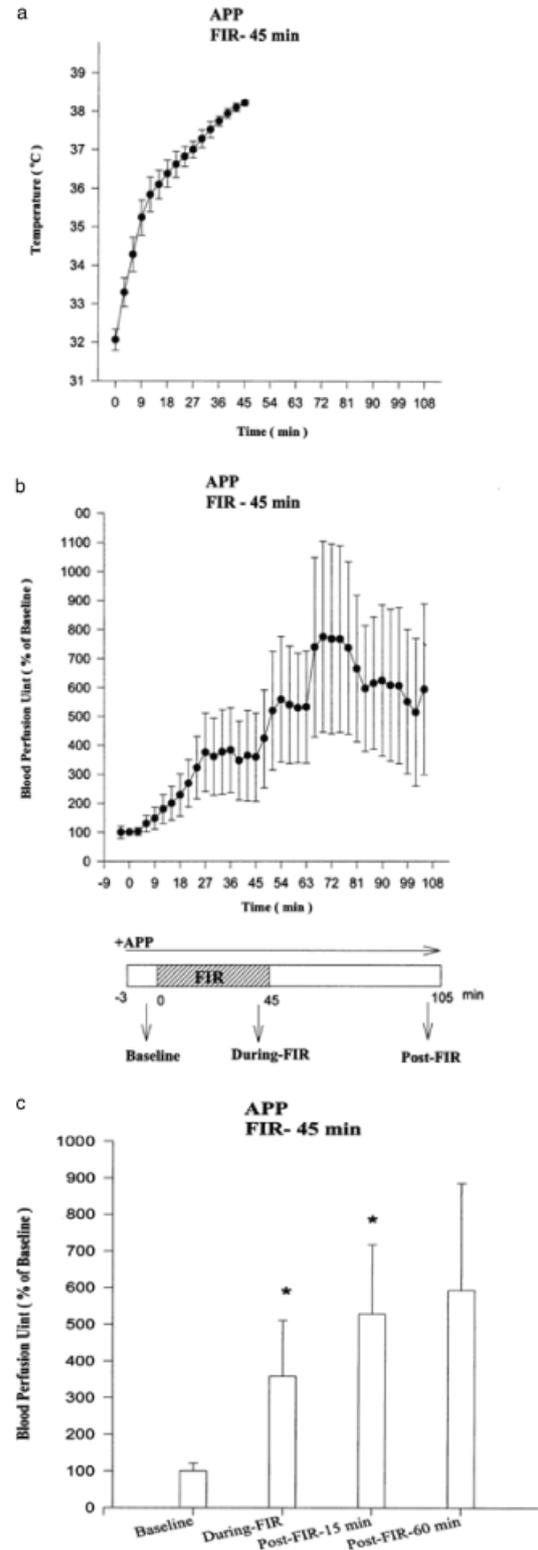
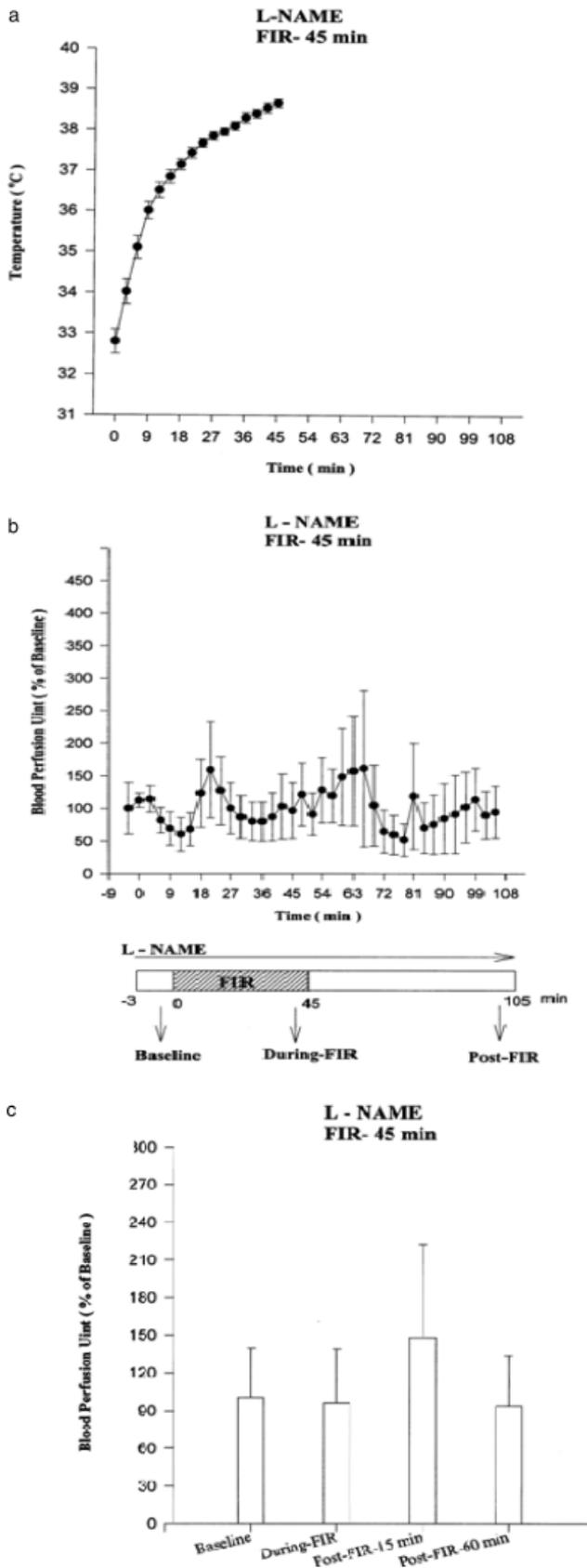


Fig. 6. (a) Effect of atropine, propranolol and phenolamine (APP) pretreatment on far-infrared (FIR)-enhanced microcirculation of rat skin. Skin blood flow increased significantly after the removal of the FIR emitter (b, c). The results suggested that APP pretreatment did not suppress the stimulating effect of FIR therapy on skin blood flow in rats. Data were presented as mean \pm SEM. * $P < 0.05$ compared with Baseline.

Discussion

The technology of FIR irradiation has been widely applied in many fields. In China and Japan, FIR has



been a versatile tool for health promotion, food preservation and food preparation. These FIR applications can be found in different products in the market, such as FIR saunas, FIR ovens, FIR incubators in maternity wards and FIR gloves. FIR can penetrate through skin and transfer energy into deep tissue gradually through a resonance-absorption mechanism of organic and water molecules (3).

Skin microcirculation plays a crucial role in improving wound healing, reducing tissue edema, relieving ischemic pain and preventing reperfusion injury. The microcirculation-impaired animal models with devascularized flap, ischemic flap and reperfusion injured flap were established and tested in previous studies (29, 33). Skin blood flow of normal rats was significantly higher than that of rats with circulatory impairment and showed a remarkable response to FIR therapy (Fig. 2). The data indicated the skin ischemic model is suitable for determination of FIR-enhanced microcirculation of the skin.

A previous study reported on the enhancement of peripheral blood circulation after acute exposure to FIR and correlated the enhancement with the hyperthermic effect of FIR treatment (34). A recent study successfully demonstrated the biological effect of FIR on promoting skin wound healing with histological evidence of greater collagen regeneration and infiltration of fibroblasts that expressed transforming growth factor-1 (TGF-1) in wounds (31). In our study, we continuously recorded skin blood flow before and during FIR therapy and, for the first time, kept measuring skin blood flow after FIR therapy to observe the post-FIR effect. During the treatment for 30, 45 or 60 min with FIR, skin temperature was steadily increased to a plateau around 38–39 °C, but skin blood flow did not fluctuate significantly. In the post-FIR recording, it was surprising to observe a significant increase in skin blood flow after FIR exposure, and the finding could be reproduced in all experimental groups. The stimulating effect of skin blood flow could be maintained for 15, 60 or 30 min after 30, 45 or 60 min of FIR therapy, respectively

Fig. 7. (a) Effect of N^G -nitro-L-arginine methyl ester (L-NAME) pretreatment on far-infrared (FIR)-enhanced microcirculation of rat skin. There was no significant elevation of skin blood flow during and after FIR treatment (b, c). In comparison to Figs 4b, c, 6b, c, the curve of skin blood flow was dampened and lost its tendency to elevate after FIR therapy. The results concluded that L-NAME pretreatment suppressed the stimulating effect of FIR therapy on skin blood flow in rats.

(Figs 3–5). The results strongly demonstrated that FIR therapy exerted a biological effect, but not a hyperthermic effect, on promoting and improving skin microcirculation.

We noticed that the skin blood flow elevated only after direct exposure to FIR, although we still do not know the exact cause. The possible explanation is that FIR induces synthesis and mobilization of biological factors, and the removal of FIR will initiate a mechanism resulting in blood flow increase. As we now know that skin microcirculation is mostly influenced by the autonomous nervous system and nitric oxide, we investigated these two mechanisms in order to explore the possible pathways of FIR effect on skin microcirculation.

The coordination of sympathetic and parasympathetic nerves regulates the skin blood flow (9–11, 35–37). Rats were intravenously pretreated with APP to determine whether the FIR-induced promotive effect on skin microcirculation was through the autonomic nervous system. Our results showed that APP pretreatment did not suppress the stimulating effect of FIR (Fig. 6) and this suggests that the promotive effect of FIR therapy on skin blood flow may not be related to the autonomic pathway.

NO synthesized in vascular endothelial cells has been claimed to play an important role in the control of blood pressure by its direct action to dilate vascular smooth muscle (12–16). NO released by endothelial cells, regulated by eNOS, induces muscle relaxation by mediating the vasodilator effects of endothelium-dependent agonists, diffusing soluble guanylate cyclase and activating the kinase-transduction chain of the smooth muscle cells of the arterial wall. Muscle relaxation dilates the vessels, decreasing the resistance to blood flow and thus increasing the local perfusion. NOS activity can be inhibited by the stereospecific molecule, L-NAME. In this study, the post-FIR enhancement of skin blood flow disappeared when rats were pretreated with L-NAME (Fig. 7). These findings can reasonably explain that FIR therapy promoted skin blood flow through a mechanism closely related to L-arginine/NO pathway.

These are pilot data with $n = 6$ in each group, and the findings here certainly merit further study with a larger number of animals.

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