# Far-Infrared Therapy for Cardiovascular, Autoimmune, and Other Chronic Health Problems: A Systematic Review

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**Abstract:** Physical therapy (physiotherapy), a complementary and alternative medicine therapy, has been widely applied in diagnosing and treating various diseases and defects. Increasing evidence suggests that convenient and noninvasive far-infrared (FIR) rays, a vital type of physiotherapy, improve the health of patients with cardiovascular disease, diabetes mellitus, and chronic kidney disease. Nevertheless, the molecular mechanisms by which FIR functions remain elusive. Hence, the purpose of this study was to review and summarize the results of previous investigations and to elaborate on the molecular mechanisms of FIR therapy in various types of disease. In conclusion, FIR therapy may be closely related to the increased expression of endothelial nitric oxide synthase as well as nitric oxide production and may modulate the profiles of some circulating miRNAs; thus, it may be a beneficial complement to treatments for some chronic diseases that yields no adverse effects.

**Keywords:** physical therapy, far-infrared (FIR), cardiovascular disease (CVD), diabetes mellitus (DM), miRNA

**Running title:** Far-Infrared Therapy for Chronic Diseases

## 1 Introduction

Infrared radiation is an invisible form of electromagnetic energy, the wavelength of which is longer than that of visible light. Infrared radiation can be categorized into 3 groups according to wavelength, namely near infrared (NIR, 0.8–1.5 μm), middle infrared (MIR, 1.5–5.6 μm), and far infrared (FIR, 5.6–1000 μm).[1] Infrared radiation probably enables multiple forms of energy to be transferred into subcutaneous tissue (approximately 2 to 3 cm deep) without stimulation or excessive heating.[2] In one study, skin temperature increased to 38–39℃ after FIR treatment for 30 min to 1 h with 20 cm of spacing between ceramic plates and the skin.[3] Thus, FIR therapy may yield none of the side effects of traditional thermal therapy, such as infection or burn injury, and has therefore been widely employed to promote health.

FIR treatment methods can be divided into two categories according to clinical implementation in general. In the first category, an FIR emitter composed of electrified ceramic plates is placed 20 cm above a patient and provides low energy to increase skin temperature steadily.[3] In addition, the FIR radiator is frequently used in experiments for local (or point) treatment by maintaining the surface temperature lower than 40℃. In the other more prevalent category, FIR dry sauna therapy,[4] light is employed to create heat by using a sauna. Unlike traditional saunas, which apply heat to warm the body by increasing the ambient air temperature, FIR saunas heat the body directly without employing the air as a heat transfer medium.[5] In a previous study, sauna therapy was performed using an FIR dry sauna device at 60℃ for 15 min, followed by traditional warm keeping for 30 min.[6]

Although previous studies have shown that FIR radiation produces thermal and nonthermal effects, such as increasing artery blood flow[7] and peripheral blood circulation,[8] improving endothelial function,[9] alleviating fatigue[10] and pain,[11] reducing blood pressure,[12] and promoting capillary dilatation,[13] the precise mechanism has yet to be thoroughly understood. Therefore, the purposes of this study were to review and summarize published data on FIR therapy on different types of disease (Table 1) and to delineate the mechanisms of FIR therapy.

## 2 FIR Therapy for Cardiovascular Disease

### *2.1 Cardiovascular Disease*

Cardiovascular disease (CVD), the leading cause of deaths worldwide, refers to any disease affecting the cardiovascular system including cerebral and renal vascular diseases, cardiac disease, and peripheral arterial disease.[14] The most common factors that induce CVD are atherosclerosis and hypertension. Moreover, even in healthy asymptomatic elderly people, various alterations in physiology and morphology affect cardiovascular function and thus result in an increased risk of CVD;[15] thus, determining treatments for curing the disease is imperative.

### *2.2 Effects of FIR on CVD*

Evidence has indicated that FIR rays exert protective effects on CVD. Several weeks of sauna therapy markedly enhanced flow-mediated endothelium-dependent dilation of the brachial artery ($P < 0.001$),[16-18] which was associated with an increase in cardiopulmonary exercise tolerance.[17,18] Because endothelial dysfunction is typically observed in patients with

hypertension,[19] hypercholesterolemia,[20] diabetes mellitus (DM),[21] and obesity and patients who smoke,[22] sauna treatments probably play a therapeutic role for patients with coronary risk factors, suggesting that sauna treatments improve vascular endothelial function.

Compelling evidence has indicated that vascular endothelial function is closely associated with endothelial nitric oxide synthase (eNOS), which catalyzes the amino acid L-arginine into L-citrulline and nitric oxide (NO) in the endothelium. NO is a crucial vasodilator substance, which prevents the progression of atherosclerosis by dilating blood vessels and inhibiting some arterial disorders such as platelet aggregation and the migration and proliferation of smooth muscle cells.[23] Ikeda et al. reported that 1 month of FIR sauna therapy significantly upregulated eNOS mRNA and protein expression (0.73 ± 0.04 vs. 1.02 ± 0.02, $P < 0.01$; 3250 ± 70 vs. 4090 ± 60, $P < 0.01$, respectively) as well as serum NO production (3.98 ± 0.43 mmol/L vs. 4.66 ± 0.5 mmol/L, $P < 0.05$) in cardiomyopathic hamsters with chronic heart failure (CHF).[24] In addition to enhancing eNOS expression, FIR increases NO production probably by promoting the $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII)-mediated phosphorylation of eNOS at serine 1179 to increase eNOS activity.[25] Although FIR radiation can notably increase the temperature of culture media and intracellular $Ca^{2+}$ levels, temperature-sensitive calcium channels and transient receptor potential vanilloid may not contribute to the pathway of the CaMKII-mediated phosphorylation of eNOS.[25] Thus, we propose that the nonthermal effects of FIR radiation, as has been recently shown for other types of nonionizing radiation,[26] may be involved in this pathway by activating voltage-gated calcium channels.[27] Nevertheless, all of these

mechanisms suggested that upregulating NO production by increasing eNOS expression level and its phosphorylation level is a critical manner in which FIR therapy improves endothelial function in patients with CHF.

Notably, urinary 8-epi-prostaglandin $F_{2\alpha}$ (a product of lipid peroxidation) levels were markedly lower in participants with coronary risk factors who received an FIR dry sauna for 2 weeks compared with those of controls.[28] Because 8-epi-prostaglandin $F_{2\alpha}$ is a reliable marker of oxidative stress in vivo, and oxidative stress is involved in the development of atherosclerosis and heart failure,[29] the results suggested that repeated FIR ray therapy can reduce oxidative stress,[30] preventing the progression of atherosclerosis. Because oxidative stress reduces the bioavailability of NO (free radicals can inactivate NO),[31] a reduction in oxidative stress probably indicates an improvement in endothelial function through an increase in NO production.

The enhancement in eNOS expression caused by FIR stimulation may be related with miRNA. Shear stress is crucial to increasing eNOS activity by stimulating its expression.[32] All of the aforementioned studies have suggested that FIR therapy accelerates peripheral blood flow, leading to an increase in shear stress, followed by increases in eNOS activity and NO production and upregulation of eNOS expression. Consequently, vascular endothelial function and exercise tolerance are improved.

A previous study reported that miRNAs are essential for various CVDs because depletion in the miRNA-processing enzyme engenders defects in cardiac development and angiogenesis.[33] Several studies have revealed that shear stress or FIR can regulate the

expression of miRNAs in endothelial cells. For instance, miRNA-21 induced by shear stress in endothelial cells can modulate endothelial cell apoptosis and eNOS activity as well as NO production.[34] In one study, miRNA-663 played vital roles in shear stress-induced inflammatory responses by derepressing inflammatory response genes.[35] A recent study determined that FIR treatment enhanced the expression of miRNA-31 and miRNA-720, thereby increasing coronary artery disease endothelial progenitor cell (EPC) expression and rescuing the angiogenic and vasculogenic abilities of EPCs both in vitro and in vivo.[36] Circulating miRNAs (e.g., miRNA-1, miRNA-17, miRNA-92a, miRNA-126, miRNA-133, and miRNA-145) in the blood cells or serum/plasma have been identified as potential biomarkers of CVD[37] and can be used for diagnosing and determining the prognosis of acute myocardial infarction.[38] In summary, we suspect that FIR improves the endothelial function of patients with CVD by increasing eNOS and NO levels by promoting shear stress and altering the expression profiles of some circulating miRNAs.

## 3 FIR Therapy for Diabetes Mellitus

### *3.1 Diabetes Mellitus*

DM is a group of metabolic diseases caused either by a deficiency in insulin production (Type 1) or by development of insulin resistance (Type 2).[39] Most diabetes cases can be grouped into two broad etiopathogenetic categories: type 1 DM, caused by failure of the pancreas to secrete insulin; and type 2 DM, caused by the inability of the body to respond properly (e.g., resistance) to insulin action or insulin secretory response.[40] A person with DM (type 1 or 2) has high

concentrations of blood sugar, which undermine the blood vessels, nerves, kidneys, and other systems of the body.[40]

*3.2 Effects of FIR on DM*

Masuda et al. demonstrated that repeated dry sauna therapy by using FIR reduced urinary levels of 8-epi-prostaglandin $F_{2\alpha}$ (an oxidative stress marker)[28] and that DM was associated with increased oxidative stress,[41] which has a marked insulin-resistance effect.[42] Kawaura et al. investigated the oxidative-stress-related modulatory effect of FIR local stimulation in bedridden patients with type 2 DM.[43] Two weeks of local FIR therapy administered to the legs significantly reduced plasma 8-epi-prostaglandin $F_{2\alpha}$ levels in type 2 DM patients ($P < 0.05$).[43] A reduction in eNOS bioactivity was involved in the pathogenesis of oxidative stress in skeletal muscle insulin resistance.[44] Furthermore, eNOS played a critical role in regulating insulin sensitivity.[45] Overall, FIR therapy may improve skeletal muscle insulin resistance through eNOS expression following a decrease in oxidative stress in patients with type 2 DM.

Patients with DM sustain stress because of daily dietary restrictions, leading to an excessive release of cortisol, causing diverse negative reactions such as hypertension.[46] Consequently, DM is exacerbated. Ryotokuji et al. indicated that 4 weeks of FIR radiation administered to the feet of type 2 DM patients significantly reduced cortisol levels and blood glucose levels.[47] Therefore, assuming that FIR therapy normalizes blood glucose levels by reducing serum levels of cortisol (adrenal glucocorticoid hormones) and thereby improves the ability to respond to insulin action in patients with type 2 DM is reasonable.

Huang et al. observed that FIR therapy increased blood flow recovery by 48%, increased bone marrow-derived EPC differentiated into endothelial cells (11.2 ± 1.1/HPF vs. 18.8 ± 2.0/HPF, $P < 0.01$), and reduced oxidative stress ($P < 0.05$) in streptozotocine-induced diabetic mice.[48] Moreover, the benefits of local FIR radiation were abolished after injection with L-NAME (an eNOS inhibitor).[48] Because neovascularization requires bone-marrow-derived circulating EPCs for vasculogenesis,[49] high glucose-impaired capacities of EPCs probably involve NO-related mechanisms.[50] In addition, NO can modify the mobilization and differentiation of EPCs,[51] and an increase in free radicals in tissue ischemia may downregulate NO bioavailability by directly inactivating NO.[31] Thus, FIR treatment may be related to a NO-related pathway. Moreover, FIR therapy is suggested to have benefits of promoting blood flow recovery and forming new vessels by enhancing the EPC homing process by reducing oxidative stress in the ischemic hindlimbs of diabetic mice.

## 4 FIR Therapy for Chronic Kidney Disease

### *4.1 Chronic Kidney Disease*

Chronic kidney disease (CKD) is a progressive renal dysfunction experienced during several months or years[52] and can be classified into 5 stages (stages 1 to 5) according to severity. End-stage renal disease (ESRD) is stage 5 CKD and is a severe illness with a poor prognosis for which treatment with dialysis or transplantation may be required.[52] For patients with ESRD who receive hemodialysis (HD) treatment, native arteriovenous fistulas (AVFs) and

prosthetic arteriovenous grafts (AVGs)[53] are typically used to obtain the well-functioning vascular access that is critical to sufficient dialysis.[54]

*4.2 Effects of FIR on CKD*

Lin et al. showed that long-term FIR exposure increased access flow (Qa), reduced the incidence and relative incidence of AVF malfunction, and improved the unassisted patency of AVFs in HD patients.[55] Because decreasing vascular access flow (Qa) is an effective index for estimating thrombosis-related access dysfunctions,[56] the improvement in the patency of AVFs was likely associated with a higher value of Qa. According to Kipshidze et al.,[57] a nonablative infrared laser (NIL) restrained neointimal hyperplasia and reduced the proliferation of vascular smooth muscle cells (VSMCs) after percutaneous transluminal coronary angioplasty in cholesterol-fed rabbits for 60 days. Because the growth of VSMCs increases the risk of vascular access stenosis in HD patients,[58] inhibiting neointimal hyperplasia may be one mechanism through which FIR therapy improves vascular restenosis progression in patients with ESRD.

Furthermore, Lai et al. investigated the effect of FIR treatment on HD access maintenance after percutaneous transluminal angioplasties (PTAs) in AVG and AVF populations.[59] The data showed that a radiated group of patients with AVGs exhibited significantly improved unassisted patency at 1 year (16.3% vs. 2.1%, $P < 0.05$).[59] However, in the AVF population, post-PTA FIR radiation therapy nonsignificantly improved the unassisted patency rate.[59] The results of clinical trials of FIR radiation therapy were inconsistent with those of Lin et al.,[55] possibly because most patients examined by Lin et al. received no PTA treatment.[55] Overall,

because of the improvement in unassisted patency, FIR radiation therapy may benefit PTA-treated AVG and AVF patients who are high-functioning or have not received repeated PTA.

The failure of an AVF to mature is a critical pathologic reason for the malfunction of newly created AVFs in people at advanced stages of CKD.[60] Lin et al. reported that 3 months of FIR treatment can enhance the rate of AVF maturation significantly (90% vs. 76%, $P < 0.05$).[61] In addition, they demonstrated that FIR stimulation provided substantial benefits of increasing access flow and the rates of AVF unassisted patency and clinical maturation as well as lowering AVF malfunction within 1 year compared with controls.[61] These results were identical to those of their previous study.[55] Endothelial dysfunction associated with AVF stenosis may lead to AVF maturation failure in HD patients.[58] In summary, FIR benefitted HD patients by promoting endothelial function in both animal[3,7,24] and clinical studies.

## 5 FIR Therapy for Ischemia

### *5.1 Ischemia*

Ischemia that triggers the unavailability of oxygen and glucose to tissues is generally ascribed to blood vessel problems, resultant damage, or tissue dysfunction. If not treated immediately, ischemia may aggravate rapidly to tissue necrosis and gangrene within several hours, potentially leading to paralysis.[62]

### *5.2 Effects of FIR on Ischemia*

A previous study determined that FIR radiation provides a strong antiinflammatory benefit to the vascular endothelium by inducing heme oxygenase-1 (HO-1) expression.[63] HO-1 is a rate-limiting enzyme in heme oxidization of biliverdin and carbon monoxide.[64] Biliverdin can be further catalyzed to a potent antioxidant bilirubin,[65] whereas carbon monoxide, similar to NO, exhibited effects of vasodilation and modulating intracellular cGMP levels in one study.[66] Thus, FIR probably plays a crucial role in increasing cGMP signaling. HO-1 was shown to prevent testis injury in models of hypoxic preconditioning.[67] Tu et al. investigated the effect of FIR postconditioning on ischemia/reperfusion (I/R) injury in rat testes.[68] The results indicated that HO-1 protein in the testes was overexpressed in a group of rats with 2 h-ischemia I/R injury treated with FIR ray therapy for 30 min compared with untreated and heat light groups.[68] In addition, administering an HO-1 inhibitor abolished the effect of FIR treatment.[68] Furthermore, FIR therapy drastically reduced apoptosis and alleviated injury of testis tissue,[68] suggesting that HO-1 is crucial in FIR postconditioning for protecting rat testis from I/R injury.

In a mouse model of an ischemic hindlimb, Akasaki et al. reported that 5 weeks of FIR sauna therapy markedly upregulated blood flow, capillary density, eNOS expression, and NO production compared with those of controls.[7] However, administering L-NAME suppressed the effects induced by FIR stimulation.[7]

FIR alleviated tissue ischemia in animal[3,7,68] and clinical studies.[69] Tei et al. reported that long-term sauna therapy reduced pain scores, increased blood flow, and promoted

angiogenesis,[69] but was ineffective in eNOS-deficient mice. In addition, exercise tolerance was upregulated.[69]

The induction of NO by eNOS is essential for regulating angiogenesis,[70] and this process can be elicited by vascular endothelial growth factor.[71-73] In summary, eNOS is a critical regulator for angiogenesis in repeated FIR sauna therapy. In addition, both eNOS and exercise can increase the mobilization of EPCs,[51, 69] which is vital to vasculogenesis.[48] Thus, FIR may be a novel innovative therapy for treating ischemic areas.

Successful revascularization of an ischemic region necessitates new blood vessel growth, stabilization, and maturation,[74,75] which are critical for reducing cell death and increasing the blood supply to damaged areas.[76] Because of the importance of pericytes in maintaining newly generated microvessels during angiogenesis, pericyte deficiency leads to endothelial cell apoptosis and destabilization of the microvasculature.[77] Thus, pericyte recruitment likely plays a key role in vascular remodeling in cortical tissues after ischemic stroke. Furthermore, a recent study reported that pericyte relaxation increased blood flow in vivo.[78] Because FIR rays enhance blood flow and improve ischemic areas, although the exact mechanism has not been elucidated, we speculate that FIR rays positively affect pericytes after ischemia.

## 6 FIR Therapy for Other Diseases

FIR therapy is effective in relieving pain in patients with chronic pain,[79] chronic fatigue syndrome,[80] and fibromyalgia.[81,82] FIR benefitted trained runners who suffered from muscle damage[83] and patients who experienced persistent and progressively increasing phantom limb

pain after amputation.[84] Furthermore, FIR stimulation alleviated depression in patients with insomnia by increasing serotonin and reducing malondialdehyde levels.[85] However, a case of pseudolymphoma occurring in a blue-green tattoo was thought to be related to FIR light exposure and induced sweating.[86] These effects on living organisms exposed to FIR rays are poorly understood; therefore, further study is required.

## 7 Conclusion and Perspectives

As a potential complementary therapy, FIR radiation had both thermal and nonthermal effects. The thermal effect of FIR therapy could increase blood flow and vasodilation by heating the tissue (hyperthermia), similar to ordinary thermal therapy composed of heat pads or hot water.[87] In addition, FIR treatment with low levels of delivered energy (nonthermal effect) also had biological activities.[88,89] A study of patients receiving hemodialysis treatment had shown decreases in stress and fatigue levels by FIR stimulation rather than thermal treatment (heat pads), which was probably attributed to the nonthermal effect.[10] A explanation of nonthermal effect of such low energy levels was that nanoscopic water layers got disturbed by low irradiances, leading to the change of cellular membrane structure, then made the therapeutic effects.[87]

Since FIR therapy was frequently applied in the medical field, numerous investigators have attempted to determine the effects of these novel FIR rays on biological systems. FIR radiation has multiple properties; thus, no direct interrelationships among the properties could be identified. Possible explanations include reduction in oxidative stress, improvement in

endothelial function, and inhibition of neointimal hyperplasia. Regarding the effect of FIR treatment on oxidative stress downregulation, Masuda et al. showed that FIR therapy reduced oxidative stress in patients with coronary risk factors.[28] In addition, a decrease in oxidative stress was observed in DM patients who received FIR therapy.[41,48] Regarding the effect on endothelial function, an intervention group exposed to FIR rays exhibited quicker amelioration of endothelial function than did nonexposed controls in both CVD[16] and CKD populations.[61] Regarding the third mechanism, Kipshidze et al. demonstrated that NIL inhibited neointimal hyperplasia.[57]

Furthermore, FIR rays have been applied in treating various chronic diseases, such as hypertension, heart failure, and vascular endothelial dysfunction, which are associated with the depletion of tetrahydrobiopterin (BH4), a critical cofactor for NO synthases.[90,91] FIR therapy improves blood flow in heated surface areas, causing an increase in vascular shear stress and enhancement of the activity of GTP cyclohydrolase I, which benefits BH4 synthesis.[92,93] Thus, the increased availability of BH4 may provide key insight into the underlying mechanisms of sauna therapy. A recent study demonstrated that capillaries control blood flow primarily related to active pericyte relaxation.[78] In addition, pericyte death in rigor results in a permanent decrease in blood flow in capillaries and damages neurons after stroke.[94-96] These mechanisms resemble FIR in improving capillary dilation and blood flow and may reflect the promotion of stroke recovery by FIR stimulation. In other words, FIR therapy may alleviate stroke by inhibiting pericyte death.

Except for the aforementioned mechanisms, the eNOS and NO-increasing activity of FIR radiation treatment may be recognized as a possible common background (Fig. 1).[97] An increase in blood flow induced by FIR treatment increases shear stress, which is a crucial determinant of endothelial function and phenotype in atherosclerosis. Furthermore, previous evidence has shown that shear stress regulated the expression of miRNAs in endothelial cells, and miRNAs influence endothelial biology by reducing apoptosis and activating the NO pathway.[34] Therefore, FIR therapy is a potential therapeutic method for treating CVD because it increases shear stress by regulating the expression of miRNA. Overall, FIR ray treatment accelerates peripheral blood flow, leading to an increase in shear stress; consequently, the miRNA levels are elevated, followed by an increase in eNOS and NO production.

The expression of NOS activity and miRNA has a circadian rhythm and is closely associated with control mechanisms governing circadian expression. Ayers et al. reported that NOS activity in the kidneys of mice exhibited a clear circadian variation. The highest level occurred during the dark period and the lowest level occurred during the light period.[98] In addition, NOS activation mediated the phase-shifting effects of melatonin and 5-hydroxytryptamine on a suprachiasmatic nuclei (SCN) circadian pacemaker in rats.[99] Moreover, as key regulators of the circadian timing process, miRNA-219 and miRNA-132 levels in SCN exhibited a salient rhythm, the highest level of which occurred during the subjective day.[100] In addition, several miRNAs are involved in the modulation of the peripheral circadian rhythm in mouse livers.[101,102] Circadian rhythms have been observed in the incidences of cerebrovascular diseases, arterial diseases, and ischemic stroke.[103,104] These

results suggested that the diurnal variation of NOS and miRNAs may be related with that of the onset of some chronic diseases. Therefore, FIR rays may have striking therapeutic effects on medical treatments on the basis of a circadian rhythm. However, further research considering objective parameters and sufficient sample sizes must be conducted in animal models and clinical applications to completely reveal the functional effect of circadian rhythms on FIR rays.

*Author Contributions*

LZ provided ideas and research directions; SSs wrote the sections on FIR therapy for CVD, FIR therapy for DM, and FIR therapy for CKD; XW wrote the sections on FIR therapy for ischemia and FIR therapy for other diseases; and JYC provided program support.

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## Table and Figure Legends

**Table Legend**

FIR, far infrared; CVD, cardiovascular disease; FMD, flow-mediated endothelium-dependent dilation; CHF, chronic heart failure; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; 6MWD, 6-minute walk distance; DM, diabetes mellitus; EPC, endothelial progenitor cell; ESRD, end-stage renal disease; Qa, access flow; AVF, arteriovenous fistula; CKD, chronic kidney disease; AVG, arteriovenous graft; PTA, percutaneous transluminal angioplasty; PAD, peripheral arterial disease; HO-1, heme oxygenase-1.

**Figure Legend**

Effects of far-infrared therapy. Far-infrared (FIR) rays enable multiple energy transfer as deep as 2 to 3 cm into subcutaneous tissue without irritating or overheating the skin and then accelerate blood flow, leading to an increase in shear stress, followed by an increase in endothelial nitric oxide synthase activity and nitric oxide production. Moreover, FIR or shear stress can regulate the expression of some circulating miRNAs in endothelial cells. Consequently, FIR therapy improves the symptoms of chronic diseases (e.g., cardiovascular disease, diabetes mellitus, and chronic kidney disease).