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Potential mechanisms for the effects of Far-infrared on the cardiovascular system: a systematic review

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Summary:

Far-infrared (FIR) is a form of thermal radiation, which may have beneficial effects on cardiovascular health. Clinical studies suggest that FIR irradiation may have therapeutic effects in heart failure, myocardial ischaemia and may improve flow and survival of arteriovenous fistula. Animal studies have suggested a wide range of potential mechanisms involving endothelial nitric oxide synthase and nitric oxide bioavailability, oxidative stress, heat shock proteins and endothelial precursor cells. However, the exact cellular and molecular mechanism of FIR on the cardiovascular system remains elusive. The purpose of this review is to discuss the current literature, focusing on mechanistic studies involving the cardiovascular system, and with a view to highlighting areas for future investigation.

Keywords: Far-infrared; endothelial function; inflammation; oxidative stress; nitric oxide

Introduction

Far infrared (FIR) is an invisible form of electromagnetic solar energy with a wavelength ranging between 3.0-1000 μm [1]. The therapeutic uses of FIR can be divided into two main categories, which have been investigated in studies contributing to a growing body of research. The first is FIR dry sauna therapy (Figure 1), which is also known as 'Waon' therapy meaning 'soothing warmth' in Japanese. This involves irradiating the entire body with FIR in a sauna (Figure 1) at 60 °C for 15 minutes, followed by a further 30 minutes covered in blankets to cause an increase in core body temperature of around 1 °C. [2, 3]. Localised FIR therapy is the other form, which typically consists of a device with ceramic plates which emit FIR irradiation when electrically heated. The emitter is usually placed 20–30 cm above the skin surface and causes a steady increase in skin temperature peaking at 38–39 °C. [4]. Over the past two decades, research has consistently suggested that FIR may have beneficial effects on a number of aspects of health, ranging from increasing the rate of wound healing to reducing breathlessness in heart failure [2, 5]. One of the major benefits appears to be in relation to endothelial function, the principal regulator of the cardiovascular system [6]. It is therefore thought that FIR may represent a potential novel, non-invasive therapeutic modality for a wide range of diseases, which have pathophysiological roots in the cardiovascular system. Most significantly in relation to clinical practice, human studies have suggested that FIR may improve patency and flow in arteriovenous fistulae (AVF) of dialysis patients and reduce symptoms of congestive heart failure [2, 7]. However, the future of FIR as a potential treatment depends on an improved understanding of a biological mechanism for its effects; something that has not yet been achieved. A number of potential mechanisms have been investigated, but none have fully explained the effects of FIR. An improved understanding of the mechanisms underpinning the apparent beneficial effects of FIR, is important to ensure that this novel, non-invasive therapy is used to maximal effect to augment current pharmacological approaches to cardiovascular disease. In this review, the current literature on FIR is summarised with a focus on effects on the cardiovascular system and cardiovascular disease, and on possible molecular mechanisms that have been identified to date. The methodology of the literature search is provided as a supplement (ESM 1).

FIR radiation

There is some debate surrounding the subdivision of the infrared spectrum by wavelength, which makes interpreting FIR studies challenging. The International Commission on Illumination describes FIR or IR-C as the wavelength between 3.0–1000 μm , whilst the alternative ISO20473 classification describes FIR as 50–1000 μm [1]. Of the studies included in this review, only a minority state the actual wavelength of irradiation produced by the FIR emitting device [7–12]. Most of the studies use a localised FIR device which produces irradiation in the range of 3–25 μm , with a peak at 5–6 μm . Whilst many of the devices used in these studies produce what would be considered mid-infrared under the ISO 20473 classification, they all meet the CIE definition of IR-C or FIR. It must be considered that the lack of exact wavelengths provided by many studies, particularly those using FIR sauna therapy makes interpretation of the results difficult. However, new units are currently being marketed which produce irradiation at wavelengths 8–14 μm and this information should be included in future studies.



Figure 1 (A) Far Infra-Red (FIR) ray device. (B) FIR suna.

Haemodynamic effects of FIR in clinical studies

The clinical effects of FIR have been examined in various clinical studies (Table I), including patients with heart failure, cardiovascular risk factors, ischaemic heart disease and peripheral arterial disease (PAD) [3, 13–22]. The majority of these are small studies examining a range of different clinical and physiological parameters and using a variety of methodologies. For example, many of the studies are randomised with a control group, but several lack a control, and all lack blinding of allocations to the subjects and investigators. Despite these flaws, there are findings suggesting a clinical benefit of FIR and some suggestion of potential mechanisms for these effects. Heart failure is the most well-researched condition with studies suggesting that both whole-body and localised FIR irradiation can improve shortness of breath and symptoms of heart failure, as well as improve endothelial function, reduce blood pressure and reduce plasma natriuretic peptides [3, 13, 17–19, 22]. The clinical benefits of FIR appear to be partly due to haemodynamic effects, including causing vasodilatation which results in reduced afterload and strain on the heart. This may also increase shear stress resulting in increased nitric oxide production by the endothelium, which is discussed later in this review. The heating effect of FIR results in vasodilatation acutely, but several of the human studies have sought to reduce the impact of this acute effect by taking final measurements the day after completing the course of FIR [3, 15, 18]. These studies still reported significant improvements in symptoms of peripheral arterial disease and left ventricular ejection fraction (LVEF) in heart failure. This goes some way to addressing the question of whether FIR has an additional effect to that of simple heating, as a delayed effect would suggest this, though studies exploring the longer-term effects and controlling for temperature are required. Another well-researched area which is less directly relevant to the cardiovascular system and beyond the scope of this review, is in relation to AVF survival and patency in haemodialysis patients. One study was included which suggested a mechanism relating to the induction of heme oxygenase-1 (HO-1) and is discussed in detail under the section on oxidative stress. As cardiovascular disease is highly prevalent in patients with chronic kidney disease (CKD), future studies in dialysis patients could seek to investigate effects of FIR on wider cardiovascular function, as well as to the localised AVF site [23]. Although, the majority of human studies have been in patients with heart failure, benefits of FIR have also been reported in patients with PAD, cardiac ischaemia and patients with cardiovascular risk factors [14–16, 20]. Patients in all of these categories stand to benefit from the haemodynamic effects of FIR, which appear to include lowering blood pressure and increasing cardiac output. The strength of conclusions that can be drawn from current human studies is fairly low as many are small trials of carefully selected patients, which lack adequate controls, randomisation and blinding. Despite this, there are findings which justify larger scale clinical trials to establish the true effects and clinical benefits of FIR in patients with cardiovascular disease.

Potential Mechanisms of FIR on the Cardiovascular System

Thus far, it has been challenging to clearly delineate the mechanism of FIR on the cardiovascular system because of the diverse range of potential mechanisms reported in various animal and cellular models, as well as in some human studies (Figure 2). FIR may exert its effects through a range of mechanisms contributing to an overall beneficial effect on the cardiovascular system. It is also possible that current studies are yet to clearly identify which, if any of these potential mechanisms plays the most important role. In this review, we have grouped the current evidence into four broad categories to highlight some of the most important potential mechanisms identified to date. These are 1) Up-regulation of endothelial nitric oxide synthase (eNOS) and increase in nitric oxide (NO) bioavailability; 2) Improvement in redox status and reduction in oxidative stress; 3) Effects on angiogenesis and endothelial precursor cells and 4) Inflammation and thrombogenesis

Upregulation of endothelial nitric oxide synthase (eNOS) and increased nitric oxide (NO) bioavailability

The endothelium, the innermost layer of the blood vessel, is considered the central regulator of vascular health [6]. The endothelium inherently produces paracrine factors to maintain vascular health. NO is one of these essential factors that regulates vascular tone along with other important functions such as inhibition of platelet aggregation and vascular smooth muscle proliferation which are vital to cardiovascular health [24]. NO is produced in endothelial cells by the enzyme eNOS [25, 26]. FIR is thought to increase eNOS expression indirectly through changes in laminar shear stress. FIR causes vasodilation, which reduces peripheral vascular resistance and afterload. This increases cardiac output and increases peripheral blood flow [27], resulting in an increase in shear stress, which is one of the most important stimuli for eNOS [25] expression. This secondary effect of increasing eNOS expression through increased shear stress appears to be partly due to a temperature effect, as FIR increases skin temperature, a known stimulus for vasodilation. However, studies have shown that the beneficial effects of FIR on endothelial function persist beyond this temporary rise in skin temperature [3, 18]. This suggests further mechanisms for a beneficial primary effect of FIR on the vasculature. There is evidence from animal studies (Table II) to suggest that FIR irradiation may cause induction of eNOS directly, which leads to increased NO bioavailability and improves endothelial function. Different experimental studies have established the increase in expression of eNOS in heart and large vessel arterial tissue following FIR irradiation in mice with hindlimb ischaemia, healthy and cardiomyopathic hamsters, and hypertensive rats [28–31]. This increase in NO bioavailability appears to contribute to improvements in the response to ischaemic states induced to mimic human coronary and peripheral vascular disease. Sobajima et al. found that FIR sauna therapy partially reduced cardiac remodeling after induced myocardial infarction (MI) in rats, while Miyauchi et al. showed improved perfusion and neovascularization in mice with hindlimb ischaemia [32, 33]. In this case, there was upregulation of heat shock protein (HSP) 90, phosphorylated Akt/protein kinase B (PKB) and phosphorylated eNOS in arterial endothelial cells within sections of ischaemic muscle. The increase in angiogenesis caused by FIR irradiation was reduced by the application of an HSP90 inhibitor, suggesting this protein is integral to the mechanism. HSP90, a chaperone protein, is a part of the family of heat shock proteins, which is produced in response to stressful conditions [34, 35] and forms a complex with Akt/PKB resulting in phosphorylation of eNOS, increasing NO production and improving endothelial function [36]. Studies examining cellular models (Table III) have shown similar effects of FIR on eNOS and provide further mechanistic information about how FIR may mediate NO production. It has been found that eNOS phosphorylation and NO production are both increased in human umbilical vein endothelial cells (HUVECs) when exposed to FIR [8]. Hsu and colleagues also showed that FIR inhibited proliferation of HUVECs induced by vascular endothelial growth factor (VEGF), with this effect peaking 30 minutes into FIR irradiation [8]. The authors claimed that heating the cells to the same extent, without applying FIR did not inhibit proliferation, although it is unclear how this heating was done without the absorption of any infrared radiation. Nitrotyrosine formation increased in HUVECs treated with FIR and VEGF. This suggests an FIR-specific effect independent of temperature, involving VEGF-induced production of superoxide anions which combine with NO to inhibit vascular proliferation. The beneficial effect of FIR on PKB/Akt and eNOS phosphorylation was abolished when phosphoinositide 3-kinase (PI3K) was inhibited, suggesting that this enzyme which is also involved in cell growth and proliferation [37], mediates FIR's modulatory effect on eNOS. FIR exposure induced the nuclear translocation of promyelocytic leukaemia zinc finger protein (PLZF), which encodes proteins regulating myelopoiesis. Again, this effect was not replicated by heating without FIR. In conclusion, it appeared that FIR induced the nuclear translocation of PLZF, which increased PI3K expression. This in turn activated PKB/Akt to phosphorylate eNOS, resulting in the beneficial end-result of increased NO production. Up-regulation of HSP90 and Akt/PKB could be an important target in treating human cardiovascular disease for a number of reasons. It results in increased phosphorylation of eNOS and NO production, which

maintains healthy vasculature and guards against endothelial dysfunction [38]. Significantly, Akt/PKB dysregulation has also been shown to promote coronary atherosclerosis through an increase in expression of pro-inflammatory genes, and to reduce postischaemic inflammatory and proliferative change in mouse models [39, 40]. Although predominantly animal models have been investigated, the evidence suggests a potential role of the Akt/PKB pathway in maintaining healthy vasculature. Based on current limited studies it is difficult to determine the importance of this mechanism in the apparent effects of FIR. If this mechanism was replicated in further animal studies and even a human study, it could suggest a potential role for FIR therapy in the treatment of cardiovascular disease, where anti-inflammatory and anti-atherosclerotic effects could impact clinical outcomes. Conflicting evidence suggests there may be several molecular mechanisms through which FIR acts to increase eNOS activity [9]. Bovine aortic endothelial cells irradiated with FIR displayed increased eNOS phosphorylation, occurring specifically at the serine 1179 site. Serine 1179 is the principal site at which eNOS regulates NO production, and phosphorylation at this site is known to be mediated by various protein kinases [41, 42]. Inhibition of protein kinase A and calmodulin-dependent protein kinase-2 (CaMKII) resulted in reduced eNOS phosphorylation, suggesting they played an integral role in the mechanism. FIR was also found to increase intracellular Ca²⁺ which modulates CaMKII activity. Overall, the experiments suggest that FIR increases intracellular Ca²⁺ causing increased CaMKII activity, which increases eNOS phosphorylation at the serine 1179 site. Furthermore, it is suggested that FIR may modulate transient receptor potential (TRP) channels, a group of cation channels permeable to Ca²⁺ that are expressed throughout the body including heart and vascular tissue. These channels act as cellular sensors and respond to a range of stimuli, including temperature. The discovery of these channels is relatively recent, but specific channels have been shown to play a role in maintaining endothelium-dependent vasodilation, so they may prove to be important targets of future cardiovascular research. In this case the activity of one thermo-sensitive channel, the transient receptor potential vanilloid channel, was investigated but its activity did not appear to be altered by FIR irradiation. The increase in CaMKII activity and intracellular Ca²⁺ shown in this study add significant information about how FIR may cause a beneficial increase in NO bioavailability, although certain aspects such as the involvement of thermo-sensitive TRP channels require further investigation. The evidence that FIR increases eNOS expression and the potential clinical benefits of this, seem to warrant further investigation. The significance of the diverse set of potential mechanisms which have been identified in the current literature is unclear, and further research is required.

Reduction in oxidative stress and increase in antioxidants

Oxidative stress occurs when there is an imbalance between anti-oxidant and oxidant production [43]. Reactive oxygen species (ROS) play an important role in physiological processes such as cell signaling and more critically in pathological ones when they are abnormally produced resulting in oxidative damage. They are involved in the pathogenesis of cardiovascular disease, including atherosclerosis and stroke [43]. These highly reactive oxidant molecules cause inactivation of NO, leading to endothelial dysfunction and cardiovascular disease [26]. Clinically, FIR has been shown to improve vascular endothelial function as measured by flow-mediated dilatation (FMD) while reducing surrogate biomarkers reflecting systemic redox status in subjects with cardiovascular conditions. Inoue et al. [13] delivered localised FIR irradiation to the legs of patients with congestive heart failure, and demonstrated a significant improvement in plasma antioxidant status. This was indicated by increased levels of antioxidants; thiol and glutathione peroxidase and reduced levels of 8-hydroxy-2-deoxyguanosine, a marker of oxidative DNA damage. Masuda et al. [14] gave FIR sauna therapy to patients with at least one coronary risk factor, including hypertension, hyperlipidaemia and diabetes mellitus. In this case, a urinary marker for oxidative stress was used, 8-epi-prostaglandin F_{2α} (8-epi-PGF_{2α}). There was a significant reduction in urinary 8-epi-PGF_{2α} levels in those receiving FIR compared with control subjects. 8-epi-PGF_{2α} opposes NO-mediated vasodilation, causing vasoconstriction, so a reduction in this urinary marker suggests FIR may increase vascular flow, shear stress and vasodilatation. Indeed, there is further clinical evidence that FIR improves endothelial function in patients with coronary risk factors, as measured by FMD [20], the gold-standard non-invasive marker of endothelial function [44]. The current body of evidence generally indicates that FIR improves cardiovascular function through reduced oxidative stress, though these studies do not address the question of the underlying mechanism for this effect, which remains unclear. Studies in animal and cellular models have sought to identify potential underlying mechanisms. Four weeks of FIR sauna therapy up-regulated cardiac expression of the antioxidant manganese superoxide dismutase as well as heat shock proteins HSP27 and HSP32 in cardiomyopathic hamsters. This was mediated by activation of cardiac phospho-p38 mitogenactivated protein kinase (pp38MAPK) which is triggered by environmental stresses [3]. HSP32, also known as heme oxygenase-1 (HO-1) catalyses the rate-limiting step in the degradation of heme to biliverdin, iron and carbon monoxide (CO). Biliverdin is subsequently reduced by biliverdin reductase to bilirubin [45]. HO-1 exerts potent anti-oxidant, anti-inflammatory, antiproliferative and anti-thrombotic effects through the end products bilirubin and CO [46]. In keeping with the previous results, a series of studies by Lin et al. have highlighted a beneficial effect of FIR on

arterio-venous fistula (AVF) for patients with CKD undergoing haemodialysis, through the induction of HO-1 [4, 7, 47]. Initial evidence from a clinical trial suggested that giving FIR irradiation over the AVF site, during dialysis three times weekly, improved vessel patency and flow [7]. A further mechanistic study examined the effects of FIR on HUVECs [7]. The expression of HO-1 protein and mRNA in HUVECs was increased in a time-dependent manner after 40 minutes of FIR irradiation, with the effect peaking between 4–8 hours and returning to baseline at 48 hours. This increase was suggested to be mediated by the thermal activation of the Change to 'nuclear factor erythroid 2-related factor 2-anti-oxidant response element (Nrf2/ARE) system.' Nrf2 is a central regulator of oxidative stress which causes transcription of important anti-oxidative target genes, including those encoding HO-1 [48]. To confirm the role of Nrf2/ARE in the effect of FIR on HUVECs, a mutation was made to the antioxidant response element (ARE), which eliminates Nrf2 activation. This abolished the effect of FIR on increasing HO-1 activation, suggesting that the Nrf2-ARE pathway is central to the mechanism by which FIR induces HO-1, and this may be responsible for beneficial effects observed in humans. Lin et al. [21] delved further into this particular mechanism by examining a naturally occurring genetic variant that affects HO-1 induction in patients receiving dialysis. A length polymorphism of the guanosine thymidine repeat in the HO-1 gene results in reduced HO-1 production [21]. Genetic testing of patients receiving FIR during haemodialysis identified the length polymorphism of either one short (S) [(GT) $n \leq 30$] or long (L) [(GT) $n \geq 30$] allele. The L/L genotype was associated with a profound reduction in HO-1 transcription and a 2.5-fold increased risk of developing AVF malfunction than those with other genotypes. The results of this study suggest that in patients with a genetic inability to produce HO-1, FIR was unable to exert a beneficial effect. This provides further evidence that HO-1 induction is involved in the mechanism of FIR, but as this study was examining changes in the AVF, an abnormal vascular bed, it is unclear whether this finding also applies to the physiological cardiovascular system. The exact interplay between FIR and oxidative stress remains unclear, and whilst some potential mechanisms for this have been identified, including the potential induction of HO-1, there are other aspects of this mechanism which require further study, such as the role of Nrf2/ARE. Clinical studies of FIR therapy in populations with high oxidative stress levels such as smokers and cardiovascular disease, with a focus on a broad range of measures of redox status as well as clinical outcomes could increase the credibility of this mechanism, while further molecular studies are needed to fully understand it.

Angiogenesis and endothelial progenitor cells

It is now understood that the process of angiogenesis, the formation of new blood vessels from endothelial progenitor cells (EPCs) which are precursor cells with the ability to differentiate into functional endothelial cells [49], occurs in adult humans as well as embryos, and acts to repair damaged blood vessels [50]. Various studies in human endothelial cells, peripheral blood and animal models suggest that FIR can mediate angiogenesis. Rau et al. [51] irradiated human microvascular endothelial cells derived from the skin for 0, 15 or 30 minutes and assessed the cells for angiogenic effects. 15 minutes of FIR doubled the degree of tube formation in the endothelial cells, which is an early marker of angiogenesis. The effect of FIR was achieved via the activation of extracellular signal regulated kinase (ERK), one of the three mitogen-activated protein kinases involved in regulating angiogenesis. Inhibition of ERK significantly attenuated the effect of enhanced angiogenesis. In contrast with studies discussed previously, there was no indication that induction of eNOS or the production of VEGF were involved. These contrasting results highlight that our understanding of FIR's interplay with EPCs remains limited. However, FIR may promote the formation of new microvasculature, which could provide collateral perfusion to ischaemic tissue, for example in peripheral arterial disease (PAD) where atherosclerosis leads to chronic ischaemia. This would be in keeping with reports that FIR can improve perfusion to the ischaemic limb and reduce symptoms in patients with PAD [49]. PAD is a common manifestation of atherosclerosis and can lead to intermittent claudication or critical limb ischaemia, with the latter resulting in limb amputation in severe cases. FIR may contribute to repairing atherosclerotic vasculature and improve collateral flow to an ischaemic limb. Shinsato et al. [15] found that FIR improved ankle-brachial pressure index and 6-minute walk distance in patients with PAD. By analysing samples of peripheral blood mononuclear cells, it was suggested that mobilization of CD34+ haematopoietic stem cells may have played a role in the clinical benefits of FIR [15]. CD34+ cells are a precursor to EPCs, so an increase in these cells could result in improved intrinsic repair of damaged endothelium. The authors also suggested that as FIR increased circulating NO and EPCs, the mechanism may be eNOS-dependent. Other studies have highlighted the role of eNOS in mobilising EPCs in angiogenesis. 13 eNOS knock out mice showed impaired neovascularization which is related to progenitor cell mobilization [52]. Since NO bioavailability is closely related to endothelial function, it can be assumed that in patients with PAD there is inadequate repair of the endothelial damage resulting in atherosclerosis and ischaemia. Therefore, induction of eNOS and increased NO bioavailability may improve the damaged vessels' inherent ability for self-repair. This study combines mechanisms relating to NO bioavailability and angiogenesis and highlights how both of these mechanisms may result in improved function throughout the diseased

cardiovascular system. It is worth noting that in contrast, Sobajima [16] unexpectedly found a reduction in CD34+ cells at the end of a course of FIR therapy. They studied patients with myocardial ischemia caused by chronic occlusion of the coronary arteries. On serial measurements of CD34+ cells throughout the FIR treatments, it was found that CD34+ numbers transiently increased during FIR irradiation but decreased towards the end of the treatment. Since there was an improvement in endothelial function and myocardial perfusion in patients receiving FIR, the reduction in CD34+ was explained by the reduction in ischaemic stimuli during FIR therapy as ischaemia is the main trigger for progenitor cells to be recruited from bone marrow to the tissues. There is clearly an unexplained interaction between FIR and CD34+ cells, and further mechanistic studies are needed to understand the precise effects on this cell type. Maintaining adequate perfusion to the peripheries is important in the management of patients with diabetes and associated PAD. Administering streptozotocin (STZ) creates a useful mouse-model of type 1 diabetes, as the drug results in an inability to produce insulin resulting in uncontrolled hyperglycaemia in the absence of exogenous insulin [53]. Huang et al. [54] studied STZ mice with unilateral hindlimb ischaemia, giving five weeks of daily wholebody FIR irradiation to the study group. Blood flow to the ischaemic limb, as measured by Doppler perfusion imaging, was improved compared to STZ mice that received body heating without FIR to control for the hyperthermic effect. It was hypothesised that FIR may affect the activity of EPCs. In mice treated with FIR, a greater proportion of EPCs differentiated into endothelial cells. FIR appeared to inhibit senescence of EPCs induced by chronic hyperglycaemia, and to reduce oxidative stress as measured by hydrogen peroxide production. A novel approach was taken by extracting human EPCs from blood, which were treated with FIR irradiation and injected into mice. This improved collateral flow recovery in the ischaemic limb. Although only limited comparisons can be drawn between an animal model and human diabetic patients, this study suggests the potential of FIR to improve collateral perfusion to the ischaemic limb by increasing EPC activity could be worthy of further investigation. Increasing the reparative activity of EPCs could also be beneficial in ischaemic disease at other sites in the cardiovascular system. Further investigation of how FIR affects human EPCs is fundamental in targeting these cells therapeutically. In one study, normal human volunteers gave peripheral venous blood samples and EPCs were isolated from total mononuclear cells [10]. The cells were treated with glucose for four days to simulate the effects of hyperglycaemia in diabetes. EPCs were then treated with FIR for 30 minutes and microarrays were done to assess for expression of various genes. FIR significantly up-regulated eNOS transcripts, in keeping with mechanisms previously discussed. More interestingly, FIR significantly up-regulated genes coding for MAPKs, Janus kinase/signal transducer and activator of transcription (JAK/STAT) and prostaglandin signaling pathways and down-regulated genes involved with cardiac fibrosis. The functional significance of this is not entirely clear, as activation of the MAPK/ERK and JAK/STAT signaling pathways has pro-inflammatory actions, which may not be beneficial to cardiovascular health [55]. FIR increased gene expression for prostaglandin signalling pathways, which could lead to increased production of prostacyclins, resulting in vasodilation and improved endothelial function [56]. Another study [11] exploring the interaction between hyperglycaemia-induced endothelial dysfunction and FIR, suggested that FIR may exert a beneficial effect by suppressing microRNA-134. Micro-RNAs are non-coding RNA molecules involved in post-transcriptional gene regulation [57]. Endothelial colony-forming cells (ECFCs), a subtype of EPCs with reparative angiogenic capabilities were collected from normal or diabetic human blood and isolated from HUVECs. MicroRNA-134 was increased in hyperglycaemic states and resulted in impaired angiogenic activity in ECFCs. When dysfunctional ECFCs were treated with FIR, then re-injected into a mouse ischaemic hindlimb, perfusion improved significantly, with a reduced effect when microRNA-134 was overexpressed. This represents another potential mechanism for the effects of FIR irradiation on angiogenic activity in endothelial cells, which could be significant if replicated in further studies. Clinical research is required to establish whether FIR has a beneficial effect on EPCs in humans and whether this is translated into an improvement in clinical outcomes in cardiovascular disease, where an improved ability to self-repair damaged blood vessels could have a significant impact.

Inflammation and thrombogenesis

Inflammation is inherently linked to the pathogenesis of cardiovascular disease [58]. Myocardial infarction, peripheral vascular disease and ischaemic stroke all stem from risk factors such as smoking and hypertension, which trigger endothelial dysfunction and lead to atherosclerosis. An anti-inflammatory effect is supported by studies discussed previously that suggest FIR upregulates HO-1, an enzyme which in addition to anti-oxidant effects, also exerts anti-inflammatory actions through the production of CO and bilirubin [7]. Lin and colleagues showed that FIR induced HO-1 enzyme activity in HUVECs, which appeared to block the expression of adhesion molecules mediated by the inflammatory cytokine tumour necrosis factor- α [7]. These adhesion molecules promote atherosclerosis by attracting macrophages to the endothelium, resulting in the formation of fatty streaks, which progress to atherosclerotic plaque. Another key pathological process in atherosclerosis and thrombosis is platelet aggregation. Investigators in Taiwan [59] showed that FIR reduced the expression of 19 genes related

to platelet aggregation in human umbilical vein endothelial cells through reduced expression of thromboxane A2 receptor. Although platelet adhesion and aggregation have an important role in thrombogenesis, measuring platelet function has not been shown to accurately predict the onset of ischaemic heart disease (IHD), so the potential clinical benefits of this may be limited.

Conclusion

This review shows that at present, there is some evidence that FIR could provide a beneficial effect to the cardiovascular system through increases in eNOS activity, a reduction in oxidative stress through the induction of HO-1, activation of endothelial progenitor cells to repair damaged vasculature and an anti-inflammatory effect. The involvement of these mechanisms appears to be independent of a direct heating effect of FIR irradiation. Within each of these categories, a number of potential mechanisms have been identified, though many are only evidenced by a single study and their significance is unclear. In some cases, the potential mechanisms identified may form part of a wider mechanism that is not fully understood. Human studies to date have focused predominantly on large vessel measures of endothelial function such as FMD, but improved microvascular flow has been shown in animal models of ischaemia and microvascular angiogenesis has been studied in cellular models. In order to establish the mechanisms of FIR on the cardiovascular system, more studies are required, as there are few robust studies and little consensus on which molecular mechanisms are most significant, as few have been replicated. Further research in humans is particularly needed, as few of the potential mechanisms found in animals have been translated into humans thus far. A clearer understanding of the mechanisms of FIR in humans is fundamental to unlocking its potential clinical benefits. Once a better understanding of the molecular mechanisms is achieved, the next step is to investigate the effects of FIR in patients with conditions such as PAD, diabetes and hypertension, for whom it could represent a novel, non-invasive therapy to augment current pharmacological and surgical approaches.

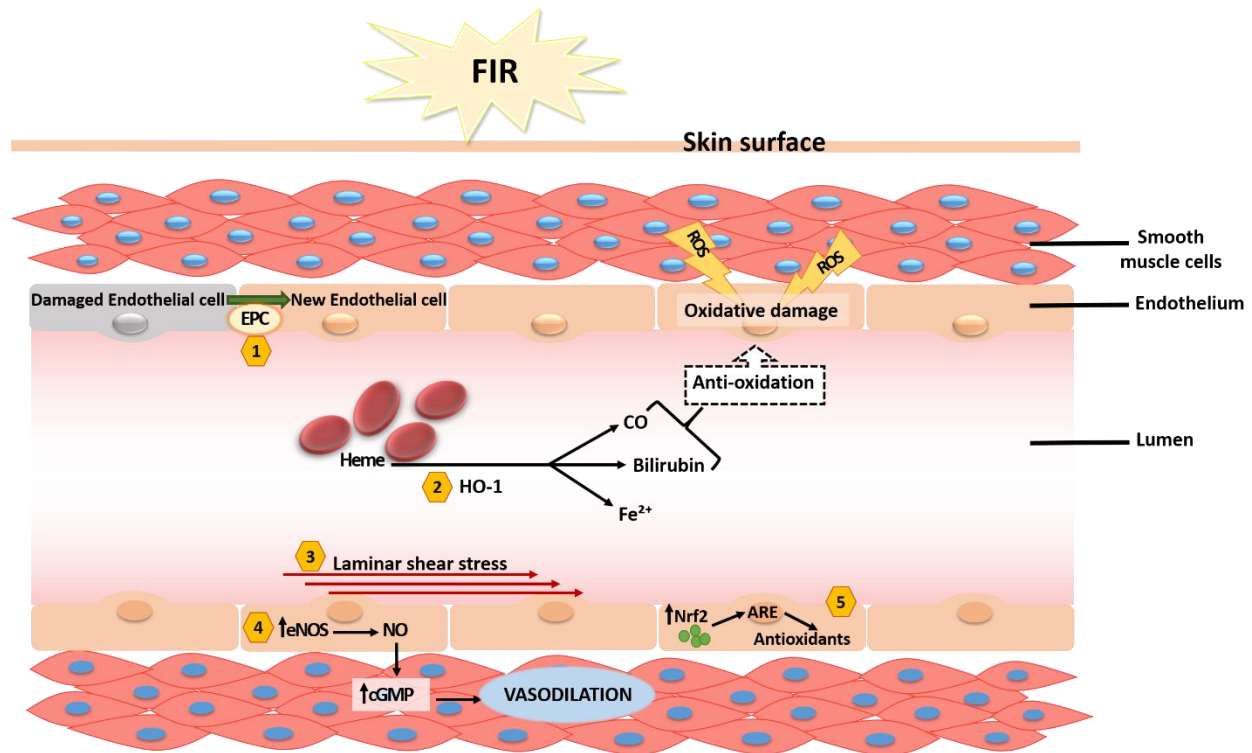


Figure 2 Summary of main mechanisms. (1) FIR increases endothelial progenitor cell (EPC) activity (precursors that differentiate into endothelial cells). (2) Upregulation of Heme oxygenase-1 (HO-1) which cleaves heme into bilirubin and CO, which both act as potent antioxidants. (3) FIR causes an increase in laminar shear stress through increasing peripheral blood flow which stimulates the expression of endothelial NO synthase (eNOS). (4) FIR directly upregulates eNOS and increases production of nitric oxide (NO) and improves endothelial function. (5) FIR might upregulate nuclear erythroid-2 like factor-2 (Nrf2) expression, a transcription factor that regulates antioxidant expression through binding to the endogenous antioxidant response elements (AREs) in the nucleus.

Table 1 Human studies examining potential mechanisms for the effects of FIR in cardiovascular disease.

Author, year	Condition	FIR delivery	Beneficial clinical or neurohumoral effect	Potential mechanism
Inoue 2012 [13]	Chronic heart failure	Localised FIR device	Improves hemodynamics endothelial function and oxidative stress	Increased antioxidants thiol and GPx and reduced oxidative stress (8OHdG)
Masuda 2004 [14]	CV risk factors	Sauna	Reduced systolic BP	Reduced oxidative stress (8-epi-PGF2 α)
Shinsato 2010 [15]	PAD	Sauna	Improved ABPI and walk distance	Increased number and mobilisation of EPCs
Sobajima 2013 [16]	Cardiac ischaemia	Sauna	Increased myocardial perfusion and endothelial function	CD34+ cells (no significant change)
Ohori 2012 [17]	Chronic heart failure	Sauna	Increased LVEF, improved FMD, Reduced plasma adrenaline, BNP	Increased CD34+ cells
Fujita 2011 [3]	Chronic heart failure	Sauna	Reduced plasma BNP, increased LVEF	Reduced oxidative stress (hydroperoxide)- Increased NO production
Miyata 2008 [18]	Chronic heart failure	Sauna	Reduced cardiothoracic ratio, plasma BNP Increased LVEF	
Kihara 2002 [19]	Chronic heart failure	Sauna	Reduced symptoms of CHF, BNP, systolic BP Improved FMD	
Imamura 2001 [20]	CV risk factors	Sauna	Reduced BP, improved FMD	
Lin 2013 [21]	CKD patients on dialysis	Localised FIR device	Improved AVF access flow and patency in patients	HO-1 (FIR had lesser effect in patients with genotype causing reduced production of HO-1)
Kuwahata 2011 [22]	Chronic heart failure	Sauna	Increased LVEF, reduced plasma noradrenaline	Reduced autonomic nervous system activity

8-epi-PGF2 α : 8-epi-prostaglandin F2 alpha; 8OHdG: 8-hydroxy-2'-deoxyguanosine; BNP: brain natriuretic peptide; BP: blood pressure; CD34+ cell: haematopoietic progenitor cell antigen 34 cell; CHF: chronic heart failure; CV: cardiovascular; EPC: endothelial progenitor cells; FMD: flow-mediated dilation; GPx: Glutathione peroxidase; HO-1: heme oxygenase-1; LVEF: left ventricular ejection fraction; PAD: peripheral arterial disease.

Table 2 In-vivo studies with potential mechanisms of FIR.

Author, year	Model	Potential mechanism and or effect
Fujita 2011 [3]	Cardiomyopathic hamsters	Increased LV contractility, reduced oxidative stress (4-HNE), Up-regulation of Mn-SOD, HSPs 27 and 32
Akasaki 2006 [28]	Mouse hindlimb ischaemia	Increased perfusion to hindlimb via induction of eNOS
Ikeda 2001 [29]	Healthy hamsters	Induction of eNOS, reduced BP
Ikeda 2005 [30]	Cardiomyopathic hamsters	Increased eNOS mRNA
Ihori 2016 [31]	Hypertensive rats	Induction of eNOS
Sobajima 2011 [32]	Myocardial ischemic rats	Inhibition of ventricular remodelling and increased vascularisation via upregulation of eNOS and VEGF
Miyauchi 2012 (33)	Mouse hindlimb ischaemia	Angiogenesis through upregulation of HSP90 which activates Akt/eNOS pathway
Huang 2012 (54)	Hyperglycaemic mice with hindlimb ischaemia	Increased angiogenesis through increased endothelial progenitor cell activity

4-HNE: 4-hydroxynonenal; BP: blood pressure; eNOS: endothelial nitric oxide synthase; HSP: heat shock protein; LV: left ventricle; Mn-SOD: manganese-dependent superoxide dismutase; VEGF: vascular endothelial growth factor

Table 3 In-vitro studies with potential mechanisms of FIR.

Author, year	Model	Potential mechanism and or effect

Lin 2008 [7]	Human umbilical vein endothelial cells	Reduced oxidative stress, Induction of HO-1
Hsu 2012 [8]	Human umbilical vein endothelial cells	Increased NO production through: Increased phosphorylation of PKB/Akt through induction of PI3K nuclear translocation of PLZF
Park 2013 [9]	Bovine aortic endothelial cells	Increased NO production through: Increased CaMKII activity and increased eNOS phosphorylation at serine 1179 site
Rau 2011 [51]	Human microvascular endothelial cells	Increased angiogenesis through ERK and p38 activation
Lin 2015 [10]	Endothelial progenitor cells from healthy human blood	Activation of JAK/STAT signalling, activation of prostaglandin signalling
Wang 2016 [11]	Endothelial progenitor cells from healthy/diabetic human blood	Increased endothelial progenitor cell activity through suppression of MicroRNA-134

ERK: extracellular receptor kinase; CaMKII: calmodulin-dependent protein kinase II; HO-1: heme oxygenase-1; JAK/STAT: janus kinase/signal transducer and activator of transcription; PI3K: phosphoinositide 3 kinase; PKB/AKT: protein kinase B/Akt; PLZF: promyelocytic.

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