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MINIREVIEWS

Non-invasive physical therapy as salvage measure for ischemic skin flap: A literature review

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Abstract

This review focuses on the available evidence regarding the molecular mechanisms and treatment potential of several non-surgical physical therapies for managing flap ischemia to propose a non-invasive, economical, and simple treatment to improve flap survival. A review of the literature was conducted on the topics of various non-invasive methods for the treatment of ischemic necrosis of the distal end of the flap between 1988 and 2019. A total of 52 published studies were reviewed on the applications of hyperbaric oxygen therapy, electrical stimulation therapy, heat stress pretreatment, phototherapy, and vibration therapy to manage skin flap necrosis. The underlying molecular mechanisms of these physical therapies on revitalizing the dying skin flaps were discussed and preliminary clinical uses of these therapies to salvage the necrotic skin flaps were pooled and summarized for clarifying the safety and feasibility of these methods. Various physical therapy regimens have been ushered to manage necrotic development in cutaneous flaps. With the refinement of these new technologies and enhancement of related basic science research on vascular revitalization, the prevention and treatment of flap ischemia will enter a new era.

Key Words: Physiotherapy; Skin flap; Hyperbaric oxygen; Electrical stimulation therapy; Heat stress pretreatment; Phototherapy; Vibration therapy

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Core Tip: In this study, the molecular mechanism of physical therapy (such as vascular endothelial growth factor, heat shock protein 32 and heat shock protein 70) was closely linked with the actual clinical application to study the effect of non-invasive physical therapy on ischemic flaps. Its effect of promoting vasodilation and regeneration as well as inhibiting cell apoptosis is also applicable to peripheral vascular lesions caused by diabetes and wound healing. The close connection between molecules and practical applications is conducive to the selection of the right physical therapy methods and parameters to achieve targeted therapy, shorten the treatment time, and alleviate quickly the pain of patients.

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INTRODUCTION

A surgical flap is a unit of transferable tissue with its own blood supply, and such flaps are obtained from various tissues ranging from simple advancements of skin to composites of many different types of tissue, which consist not only of soft tissue but also of skin, muscle, bone, fat, or fascia. Flap surgery can be traced back to 600 BC when Sushruta Samita first performed a nasal reconstruction using a cheek flap. Since then, the evolution of flap surgery has gone through different phases from attempts to use an advancement flap on an adjacent defect area and distant pedicle flaps to the other area of the body during the Renaissance period to free tissue transfer in the 1960s, the development of fasciocutaneous, osseous, as well as osseocutaneous flaps in the 1980s, and the introduction of perforator flaps in the 1990s, which altogether have changed the field of reconstructive surgery. Currently, flap surgeries are widely performed to repair skin defects caused by skin and subcutaneous tissue injuries.

The postoperative survival of a flap depends on the abundance of oxygenated blood in the distal edges of the flap. Perfusion of blood through the vascular plexuses decreases with increasing distance from the feeding artery or arteriole; thus, the distal parts of the flap are the most vulnerable to ischemic necrosis, which, as a serious postoperative complication, must be meticulously managed. Although surgical methods remain the most effective treatment options, other non-surgical methods, including physical therapies and pretreatment with physical factors, growth factors, and medications, have been practiced to promote flap survival[1-4]. This article attempts to review the available evidence on the methods, related mechanisms, and effects of non-surgical physical therapies for managing flap ischemia in order to propose a non-invasive, economical, and simple treatment to improve flap survival.

HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen (HBO) therapy refers to a non-invasive physical treatment that increases arterial and tissue oxygen tensions in the environment with an atmospheric pressure higher than normal pressure, which allows more oxygen *per* liter of blood to be delivered to increase the oxygen content in the blood, subsequently promoting the diffusion of oxygen throughout the tissue and improving aerobic metabolism and microcirculation in the tissue[5]. Since HBO was introduced for flap salvage in cases of ischemic complications in clinical practice, various studies have elucidated the underlying mechanism by which HBO improves flap survival as described below[6].

Improving circulation and accelerating angiogenesis

Zamboni *et al*[7,8] measured the blood flow in the microvasculature of the skin flap with laser Doppler (LD) flowmetry and observed a significant increase in the blood flow in the micro-vessels of the ischemic flaps following HBO treatment. Ulkür *et al*[9] also suggested that HBO treatment effectively increases the percentage of flap tissue that survives as well as the mean LD flow along the axial direction of flaps with

various forms of vascular insufficiency. This therapy is most effective for flaps with arterial insufficiency.

Furthermore, Sheikh *et al*[10] demonstrated that the underlying molecular mechanism of HBO is enhanced secretion of vascular endothelial growth factor (VEGF) to promote the proliferation of vascular endothelial cells. Furthermore, Hood *et al*[11] showed that VEGF can induce endothelial cell isoforms to express nitric oxide synthase and promote the synthesis of nitric oxide. These results indicate that VEGF-induced vasodilation, angiogenesis, and increased vascular permeability are important mechanisms by which HBO improves recovery of an ischemic flap.

Increasing tissue oxygen partial pressure and oxygen absorption on the surface of the skin flap

Hjortdal *et al*[12] studied the relationship between partial oxygen tension of the flap and blood flow in the tissue, oxygen tension, oxygen delivery, and oxygen consumption in 24 porcine island musculocutaneous flaps and showed that HBO improved both blood supply and oxygen consumption in the flaps. Mathieu *et al*[13] applied hyperbaric pressure and monitored transcutaneous oxygen pressure and ischemic flap perfusion, finding that transcutaneous oxygen pressure monitoring in a hyperbaric environment can precisely predict the survival of ischemic flaps. Considering these two studies together, we propose that a hyperbaric environment can promote the permeability of the skin to oxygen to improve further the postoperative survival of the flap by addressing the increased demand for oxygen.

Lessening ischemia-reperfusion injury

Ischemia-reperfusion (IR) injury is defined as repeated ischemic injury caused by the reperfusion of blood flow to the microvasculature in initially ischemic tissues. Pathogenically, microvascular contraction with neutrophil adhesion and infiltration underlies the mechanism of IR injury. In a study to understand comprehensively the therapeutic potential of HBO in managing IR injury, Godman *et al*[14] found that HBO can upregulate genes related to antioxidant, cytoprotective, and early antioxidant pathways in the context of IR injury in order to protect endothelial cells from oxidative damage. Gurer *et al*[15] further demonstrated that HBO can reduce the post-IR process of oxygen free radical-induced peroxidation. Zamboni *et al*[16] showed that HBO can also inhibit the adhesion of neutrophils, β2-integrin, and CD18 surface molecules to vascular endothelial cells in rat skeletal muscle pedicle flaps to improve flap survival. Taken together, these findings indicate that although IR injury shortens the survival of free flaps, HBO treatment may reverse or limit this process.

Clinically, HBO has now been used to manage the survival problem of ischemic skin grafts or flaps[17,18], Francis and Baynosa[19] concluded that HBO should be administered for salvaging failed flaps at 2.0–2.5 atmospheres absolute from 90–120 min twice daily initially and then transitioned to once per day when clinical assessment and other analyses such as transcutaneous oximetry or LD show improvement in the viability, vascularity, and tissue stability of the flaps.

However, patients should be aware of the risks and complications of HBO therapy before undergoing the therapy. Although the most common adverse events, such as claustrophobia, barotrauma of the ears or paranasal sinuses, and transient changes in vision, are all benign complications, HBO therapy does carry some risk of serious complications related to the side effects of either oxygen or pressure. Clinically, oxygen can have toxic effects on the pulmonary, ocular, and neurological organs, while pressure can induce barotrauma to damage every enclosed and air-filled cavity, including but not limited to the lungs, ears, sinuses, and intestines[20]. Therefore, informed consent from patients and their families should be obtained in advance with careful explanation of the risks of this therapy.

ELECTRICAL STIMULATION THERAPY

As a commonly used physical therapy method in clinical practice, electrical stimulation can ameliorate the ischemic state and improve the survival chance of flaps by inhibiting the vasoconstrictive effect of sympathetic nerves[21] and other mechanisms as described below.

Dilating blood vessels and boosting blood circulation

Machado *et al*[22] showed that Transcutaneous Electrical Nerve Stimulation can

expedite the healing of skin wounds in rats by increasing the skin temperature and blood flow, which may induce the release of vasodilatation-related neuropeptides such as substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide. Lobov *et al*[23] used LD flowmetry to confirm a significant increase in skin blood flow in the lower leg after bidirectional pulsed transcutaneous spinal cord stimulation at 30 Hz, thereby suggesting that NO as an important mediator promotes vasodilatation and increased skin blood flow during transcutaneous spinal cord stimulation. Taken together, these studies indicate that electrical stimulation not only has an inhibitory effect on sympathetic nerves but also dilates blood vessels and promotes blood circulation through the induced release of vasodilators.

Expediting angiogenesis

Chen *et al*[24] studied the effect of an electric field (EF) on endothelial cell neogenesis in three-dimensional culture and found that the formation of the vascular lumen was significantly increased after endothelial cells were placed in an EF for 4 h. Moreover, the length of the vascular tubule was elongated in a dose-dependent manner following a 6-h incubation with an EF intensity of 50-200 mV/mm. At the molecular level, the EF in three-dimensional culture enhanced the expression of VEGF in endothelial cells and also activated VEGF receptor-2, serine/threonine kinase (AKT), extracellular regulated kinase 1,2, and c-Jun NH2-terminal kinase signaling, indicating an important role of the VEGF-VEGF receptor-2-AKT signaling pathway in EF-induced angiogenesis.

Bai *et al*[25] further proposed that the basis of angiogenesis is migration, proliferation, and elongation of endothelial cells, and their ability to arrange into tubules in three-dimensional space. To understand comprehensively the molecular mechanism of EF treatment, four different types of vascular endothelial cells were cultured in an EF for 24 h. The dynamic behavior of the cells was recorded and analyzed with an image analyzer, and the results showed that human microvascular endothelial cell-1 possessed the greatest directional migration potential and was most closely related to neovascularization. From the above studies, it can be seen that compared with macrovascular endothelial cells, the microvessels at the skin or limb ends are more sensitive to electrical stimulation and play a role in neovascularization by secreting angiogenesis-related growth factors.

Enhancing skin regeneration, inhibiting apoptosis, and facilitating inflammatory cell migration

One study investigated the ability of a pulsed EF to promote the repair of skin in aged rats and showed that the EF at the tissue level increased the synthesis of proteins as well as the permeability of the skin for small deoxyribonucleic acid and ribonucleic acid, thereby facilitating the regeneration of the skin[26]. In another experiment, external electrical stimulation could cause a stress response in organisms to enhance the expression of stress-related protein-heat shock protein (HSP) 70, which inhibits the apoptotic process in ischemic flaps[27,28]. Additionally, Kloth[29] reported that conductive stimulation allows macrophages associated with the inflammatory response phase to migrate to the anode, while fibroblasts and human keratinocytes associated with the proliferation and remodeling phase migrate to the cathode. Thus, the EF can be used to generate this directional migration effect to control the inflammatory response and accelerate flap healing.

Electrical stimulation has been shown to improve the survival of ischemic flaps through animal (rat) experiments with the use of EFs with high-frequency and high-intensity currents (80 Hz, 15–20 mA)[4,30-33]. When EF therapy is recommended for patients, the stimulation intensity is suggested to set at three to four times more than the sensing threshold[34,35], so it is inferred that high-intensity stimulation is an effectiveness-determining factor in improving flap survival regardless of frequency or current.

Although electrotherapy is convenient and inexpensive, the body is prone to adapt to the therapy quickly. Therefore, it needs to be performed by well-trained medical staff who can precisely set electrotherapy-related parameters and determine placement sites for electrodes as well as treatment intervals, all of which vary from person to person and require timely adjustments[36].

HEAT STRESS PRETREATMENT

For heat stress pretreatment, various methods are used to thermalize the body surface wholly or locally to 40-45 °C in order to induce the synthesis of a highly conserved

HSP[37], which possesses anti-ischemia and anti-hypoxia effects to prevent tissue injury by other harmful factors and maintain tissue cell activity. The possible mechanisms by which heat stress pretreatment benefits ischemic flaps through HSP induction are discussed below.

Increasing the secretion of HSP70 to halt the apoptotic process

Rinaldo *et al*[38] applied heat stress treatment to cultured endothelial cells and observed that HSP70 synthesis began after 2 h, increased significantly after 4 h, and reached a peak after 8-24 h. Harder *et al*[39] showed that local thermal pretreatment significantly reduced necrosis and apoptosis of ischemic flaps in pigs. Upon immunohistochemical staining for HSP70, the pretreated skin displayed more uniform and constant staining (brown nuclei and cytoplasm) in comparison with that of the control group. Other studies have also indicated that HSP70 can antagonize and neutralize apoptosis-inducing factors, block the assembly of functional apoptosomes, prevent activation of stress kinases (endonucleases), and protect against the proteotoxic effects associated with adenosine triphosphate consumption[40-44].

Secretion of HSP32 for advancing the microvasculature expansion

It has been demonstrated that thermal pretreatment can cause arteriolar dilatation, which can significantly increase blood flow and perfusion of capillaries while lessening the degree of inter-tissue edema and ischemic necrosis[37]. Harder *et al*[45] observed a significant increase in the expression of HSP32 in dorsal flaps of mice in response to heat shock pretreatment and confirmed that the increase in blood perfusion in ischemic flaps after heat pretreating is associated with arteriolar dilatation caused by the increase in carbon monoxide production induced by HSP32. Therefore, the increased secretion of HSP32 caused by heat pretreatment greatly improves the survival chance of flaps by increasing flap hemoperfusion and expanding arterioles.

Heat-related physical therapy is often applied after a flap surgery in clinical practice. However, theoretically, if hyperthermia could be applied before flap surgery (24 h prior) to increase the local secretion and accumulation of HSP, the necrosis rate of the flap could be greatly reduced[39].

Hyperthermia can be applied to the necrotic flap with a short therapeutic time and simple operational requirements but is contraindicated in patients with acute inflammation and high fever. Zhou *et al*[46] warned that continuous high temperature could increase neurotoxicity, and toxicants from continuous exposure to 40.5 °C can trigger significant autophagy beyond the protective mechanisms of the body[46].

PHOTOTHERAPY

Photobiotherapy, also known as low-level laser therapy, is a non-invasive and safe treatment that can be used to treat various diseases, including surgery, tumors, oral diseases, and skin diseases. Ma *et al*[47] studied the effect of 810 nm near-infrared laser treatment on the revascularization of ischemic flaps and found that the survival rate of ischemic flaps that were irradiated with laser was significantly higher than that of the control group. Moreover, the irradiated flaps had a clear tissue structure and less inflammatory cell infiltration on hematoxylin and eosin staining, and the numbers of arterioles and capillaries in the irradiated flap were significantly greater than those in the control group based on staining for α-smooth muscle actin and factor VIII. Additionally, Martignago *et al*[48] applied a low-level laser (660 nm) to random flaps and found that rats treated with a low-level laser had a significant decrease in the area of flap necrosis and a significant increase in collagen synthesis compared with the control group. However, no increases in the expression of transforming growth factor-β and fibroblast growth factor, which are closely related to the regulation of angiogenesis and collagen synthesis, were observed in the same study, suggesting the depth of low-level laser action is too shallow to unleash any effect on deep tissue.

Low power He-Ne lasers have been used clinically to prevent as well as treat skin infections and promote wound healing. However, because the depth for the function of the low-level laser is shallow[49], causing it have to have less effect on deep tissue, this approach needs to be combined with other physical therapies such as electrical stimulation and HBO therapy if the flap is thick.

VIBRATION THERAPY

Ameliorating local circulation

In their research, Lohman *et al*[50] confirmed that short-term low-frequency vibration can increase the cutaneous blood flow in the lower limbs with or without contractile movements of muscles and further proposed that vibration can increase the activity of endothelial nitric oxide synthase, which leads to an increase in nitric oxide concentration, and then promote the expansion of skin blood vessels. In animal models, vibration therapy has been shown to improve microcirculation in various tissues and organs in young pigs[51].

Elevating the production of wound healing-related growth factors and chemokines

Weinheimer-Haus *et al*[52] investigated the effect of low-intensity vibration (45 Hz) on wound healing in the skin of diabetic mice and demonstrated that low-intensity vibration increased the expression of wound healing-related growth factors and chemokines (insulin-like growth factor-1, VEGF, and monocyte chemoattractant protein-1), which in turn promoted angiogenesis and granulation tissue formation.

At present, vibration therapy is used to improve sensory disturbance and reduce muscle tension in clinical practice[53], and it is believed that its role in promoting blood circulation and wound healing can also be applied in the field of flap surgery.

In addition to the above more commonly used physical therapies, other novel treatment methods such as shock wave therapy[54,55] and cryotherapy[56] have been investigated for the management of ischemic flaps.

CONCLUSION

In conclusion, various physical therapy regimens have been used to manage necrotic development in cutaneous flaps (Table 1). Methods for inhibiting the vasoconstrictive effect of sympathetic nerves and many related proteins such as VEGF, HSP32, and HSP70 and their pathways have been studied (Figures 1 and 2). However, none of these treatments can completely treat and prevent necrosis of the flap. Additionally, whether these physical therapy regimens can be established as targeted therapies and how they can be effectively combined to achieve the best effects requires more well-designed studies. It is believed that with the development and expansion of clinical technologies and basic research, the prevention and treatment of flap ischemia will enter a new era.

Table 1 Reported studies of physical therapies for managing ischemic flaps

Physical method	Year	Research species	Main findings	Ref.
Hyperbaric oxygen	1989	Rats	HBO treatment increased the percentage of surviving axial pattern skin flap when administered during or immediately after total flap ischemia. The improved flap survival appeared to be a systemic and not a local effect	Zamboni *et al*[7]
	1992	Rats	HBO treatment of ischemic rat skin flaps improved distal microvascular perfusion as measured by laser Doppler flowmetry. This effect was observed for HBO treatment given either during or immediately after prolonged global ischemia	Zamboni *et al*[8]
	1993	Rats	HBO treatment did not exacerbate reperfusion injury but rather appeared to protect the microcirculation by reducing venular leukocyte adherence and inhibiting progressive adjacent arteriolar vasoconstriction	Zamboni *et al*[16]
	2002	Rats	HBO treatment increased the survival length and mean LD flows of axial pattern skin flaps with all types of vascular insufficiency	Ulkür *et al*[9]
Electrical nerve stimulation	1988	Rats	High-intensity (20 mA), high-frequency (80 Hz) TENS applied segmentally at the base of the flap was shown to be the most effective treatment for increasing the flap survival	Kjartansson *et al*[31]
	1988	Human	ENS increased peripheral blood flow and prevented necrosis in ischemic flaps	Lundeberg *et al*[34]
	1990	Human	Local blood flow in skin flaps was significantly increased by ENS, but not by placebo. Repeated ENS treatment reduced stasis and edema significantly, and the capillary refill was also significantly improved	Kjartansson *et al*[35]
	1997	Rats	The flap survival area did not increase with EA but increased significantly with TENS treatment, and blood flow in the periphery was significantly greater than that at the base	Niina *et al*[32]
	2003	Rats	TENS was significantly more effective at increasing the survival of random-pattern skin flaps than topical nitroglycerin or nothing	Atalay *et al*[30]
	2006	Rats	TENS with an amplitude of 15 mA (80 Hz) produced a lower necrotic area than observed in the control group and was efficient at increasing random skin flap viability	Liebano *et al*[33]
	2008	Rats	Low-frequency (2 Hz, 15 mA) TENS treatment was effective at improving the viability of ischemic skin flaps	Liebano *et al*[57]
	2015	Rats	Electrical stimulation applied to the normal area before flap elevation increased flap survival	Doğan *et al*[4]
Heat stress preconditioning	2004	Pigs	Local heat preconditioning may be helpful for reducing wound healing complications related to ischemia following surgical dissection. The effect may be mediated by the induction of HSP70 expression	Harder *et al*[39]
	2005	Mice	Local heat preconditioning of myocutaneous tissue markedly increased flap survival by maintaining adequate nutritive perfusion rather than inducing ischemic tolerance. The protection was caused by increased arteriolar blood flow due to significant arteriolar dilation, which was mediated through the carbon monoxide-associated vasoactive properties of HSP32	Harder *et al*[45]
Phototherapy	2018	Rats	Photobiomodulation therapy with an 810-nm near infrared laser enhanced ischemic flap revascularization and increased flap viability	Ma *et al*[47]
	2019	Rats	Laser photobiomodulation at three points of the flap cranial base was more effective than at that 12 points for reducing the necrotic area	Martignago *et al*[48]
Shock wave therapy	2009	Rats	Preoperative ESWT may enhance skin flap survival in a rodent model	Reichenberger *et al*[55]
	2011	Rats	Preoperative ESWT improved skin flap survival through enhanced topical blood perfusion and neovascularization *via* elevation of angio-active factors	Keil *et al*[54]
Cold therapy	2005	Mice	Experimental cooling-induced preconditioning attenuates skin flap failure; this was associated with the increased expression of HO-1	Kubulus *et al*[56]

EA: Electroacupuncture; ENS: Electrical nerve stimulation; ESWT: Extracorporeal shock wave therapy; HBO: Hyperbaric oxygen; HO-1: Hemeoxygenase-1; LD: Laser Doppler; TENS: Transcutaneous electrical nerve stimulation.

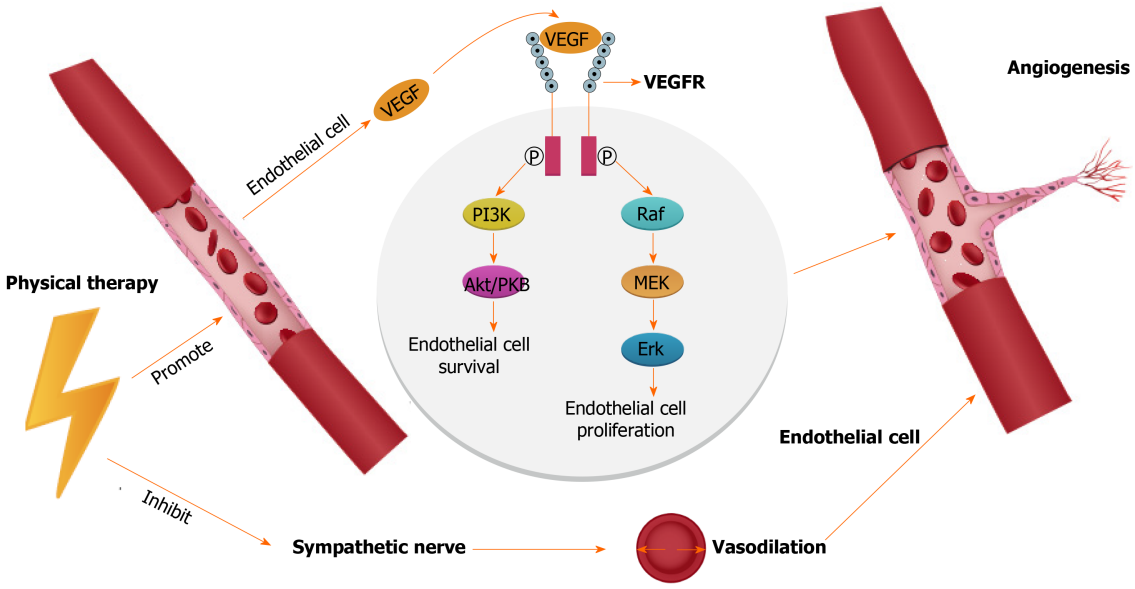

Figure 1 Putative mechanism of physiotherapy on the dying skin flap as induction of angiogenesis through inhibiting sympathetic nerve for vasodilation and promoting the secretion of vascular endothelial growth factor secretion. Akt/PKB: Protein kinase B; Erk: Extracellular signal-regulated kinase; MEK: Mitogen-activated protein kinase kinase; PI3K: Phosphatidylinositol 3-kinase; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; Raf: Rapidly accelerated fibrosarcoma.

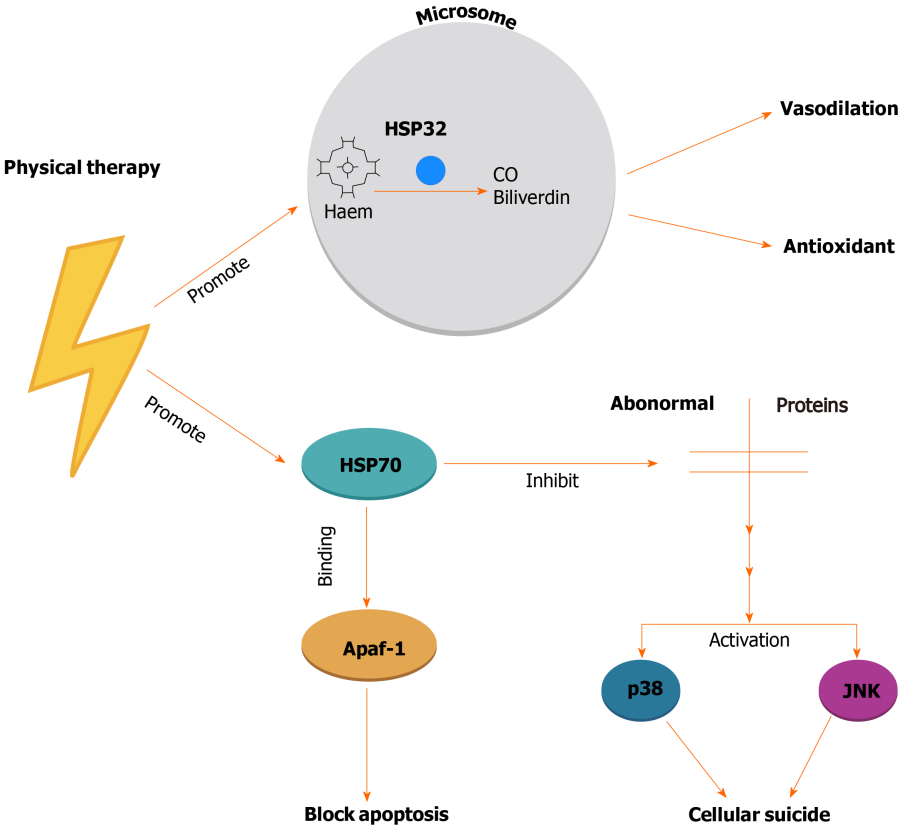

Figure 2 Putative molecular mechanism of physiotherapeutic methods for upregulation of heat shock protein 32 and heat shock protein 70 in the skin flap, which promotes vasodilation and inhibition of apoptosis. Apaf-1: Apoptosis protease-activating factor-1; HSP: Heat shock protein; JNK: Jun N-terminal kinase; p38: Protein 38.

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