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REVIEW ARTICLE

Intermittent Pneumatic Compression Devices – Physiological Mechanisms of Action

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There are many reports of how IPC is used effectively in the clinical setting; including the prevention of deep venous thrombosis, improvement of circulation in patients with lower extremity arterial diseases, reduction of lymphoedema, and the healing of venous ulcers. However, despite the widely accepted use of IPC, it is still unclear how IPC actually exerts its beneficial effects. The exact physiological mechanisms of action are unknown. The clinical utility of IPC and the putative mechanisms by which IPC could exert its therapeutic effect will be reviewed. The paper will examine the mechanical effects of IPC exerted on the lower extremity, and the subsequent biochemical changes in the circulation. In vitro *studies of the effects of mechanical stress such as compressive strain and shear on cultured endothelial cells, and their clinical relevance to IPC will also be reviewed.*

Key Words: Pneumatic compression; Mechanical stress; Fibrinolysis; Prostacyclin; Cyclic strain; Shear stress; Venous insufficiency; Deep venous thrombosis; Arterial insufficiency; Venous stasis; Plasminogen activator inhibitor; Tissue factor pathway inhibitor; Tissue plasminogen activator.

Introduction

As early as the 1800s, physicians have experimented with the concept of improving blood circulation by exerting external pressure on the legs. There were many documented uses of an assortment of suction devices to treat diseases ranging from cholera to thromboangiitis obliterans.[1–3] In 1934, Mont Reid and Louis Herrmann proposed the use of alternating pressure and suction in what they called, "PAVAEX" (Passive vascular exercise), to treat various forms of lower extremity arterial diseases. They devised an apparatus that consisted of a control box and a chamber. Patients placed their lower extremity into this chamber, which then subjected the limb to various amounts of negative and positive pressure. Reid and Herrmann noted that cycling 20–40 mmHg of positive pressure with 80 mmHg negative pressure over 20 s improved arterial circulation in patients suffering from arteriosclerosis and thromboangiitis obliterans, Raynaud's disease, and foot ulcers.[4] Landis and Gibbon expanded this use of pressure-suction technique to include the treatment of ischaemic limb, chronic ulcers, and claudication.[5,6]

Today, intermittent pneumatic compression (IPC) devices are primarily used in the prevention of deep venous thrombosis (DVT). Less common uses of IPC include the treatment of venous ulcers, lymphoedema, venous insufficiency, arterial occlusive disease, prevention of haematoma, pretibial mucinosis, and giant haemangiomas (Table 1). However, despite the widely accepted use of IPC for the treatment of arterial and venous diseases, it is still unclear how IPC actually exerts its beneficial effects. The exact physiological mechanisms of action are unknown. This paper will review the clinical utility of IPC and the putative mechanisms by which IPC could exert its therapeutic effect.

Methods

We employed Medline searches using keywords such as "pneumatic compression", "mechanisms of action",

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Table 1. Clinical utility of intermittent pneumatic compression.

Prevention of deep venous thrombosis
Orthopaedic surgery[7–9]
General surgery[12]
Cardiothoracic surgery[11]
Neurosurgery[10]
Urology[12]
Gynaecologic surgery[12]
Vascular surgery[12]
Treatment of lymphoedema[13,14]
Postmastectomy
Post radiation treatment
Arterial occlusive disease[15]
Miscellaneous
Prevention of haematoma[17]
Venous ulcers[16]
Chronic venous insufficiency[16]
Pretibial mucinosis[18]
Giant haemangiomas[19]

or "fibrinolysis". Once we had an idea of the various proposed mechanisms of action, we searched for relevant papers pertaining to mechanical strain or shear that relates to the various mediators listed as possible agents relevant to the therapeutic effects of IPC.

Clinical efficacy

IPC is well known as a treatment option for a variety of circulatory diseases. However, the most widely accepted application of IPC has been for the prevention of DVT and subsequent thromboembolism. IPC is an important modality for DVT prevention in patients undergoing various surgical procedures or in patients who have sustained serious trauma.

One of the most widely reported successes in using IPC for DVT prevention is in patients undergoing orthopaedic surgery procedures. DVT has been reported to be as high as 70% in orthopaedic patients who did not receive any prophylactic preventive measures. Pulmonary embolism occurred in up to 6% of these patients and fatal pulmonary embolism in as many as 3.4%.[7] In a study of 425 patients who underwent total hip arthroplasty, the use of intraoperative and postoperative thigh-high IPC combined with duplex ultrasound was effective for prophylaxis against DVT and thromboembolism. Furthermore, the reported low rate of DVT (4.6%) and symptomatic PE (0.6%) was comparable to the low prevalence achieved with pharmacological prophylaxis.[8] Similarly, in a study of 104 patients undergoing either joint replacement or fracture repairs, the rate of DVT was reduced from 19% in the control group to 2% in the group treated with IPC.[9]

The successful use of IPC in the prevention of DVT and pulmonary embolism has also been well documented in a variety of surgical procedures. In 128 patients who underwent craniotomy, IPC reduced the incidence of venous thrombosis from 9 of 49 control patients (18.4%) to 1 of 53 (1.9%) patients treated with IPC.[10] Moreover, in a study of 2551 patients who underwent cardiothoracic surgery over a 10-year period, combining the use of bilateral IPC and subcutaneous heparin reduced the frequency of postoperative pulmonary embolism by 62% compared to the prophylactic use of subcutaneous heparin alone.[11] In a study of 500 patients in five surgical specialties (general surgery, gynaecological surgery, orthopaedic surgery, genitourinary surgery, and vascular surgery) using several modalities of DVT prophylaxis, the incidence of DVT in the control group was 35.6%, while the incidence within the heparin, graduated elastic stocking and IPC groups were 25.5%, 14.2%, and 11.5%, respectively.[12]

IPC has also been utilised in the treatment of lymphatic disorders. In a study of 28 women previously treated for breast cancer, manual lymph drainage and IPC were equally efficient in decreasing arm volume.[13] IPC treated patients had a 25% observed reduction in circumference of limb oedema compared to 20% in the control group.[14]

Peripheral arterial disease is another area in which IPC has been used. Intermittent pneumatic foot compression (IPC_{foot}) has been utilised in treating symptomatic lower extremity claudication. In a study of 37 patients with symptomatic claudication, 25 patients received IPC_{foot} treatments at least 4 h per day for 4.5 months. When compared to the 12 controls, the treated group increased claudication distance by over 100%, their resting-ankle brachial index (ABI) by 18%, and post exercise ABI by 110%. Moreover, the treated group increased arterial calf inflow by 36%, which suggested an improved collateral circulation. Maximum benefit from this treatment was most evident in the first 3 months. Improvement in arterial circulation in some patients was maintained even 1 year after treatment.[15]

For the treatment of venous ulcers secondary to venous insufficiency, 21 of the patients received IPC and the healing efficiency of these treated patients were compared to 24 non-treated patients. Only one of 24 patients in the control group had complete healing of all venous ulcers compared with 10 of 21 patients healed in the IPC group. The median rate of ulcer healing in the control group was 2.1% area per week compared to 19.8% area per week in the IPC group.[16]

Another novel use of pneumatic compression includes the prevention of haematoma after varicose vein stripping. When IPC was applied with a compression of 40–50 mmHg then held for 24–36 h, the patient could walk and the pneumatic compression prevented post-varicose vein stripping haematoma formation.[17] More controversial uses of PC include its use in treating pretibial mucinosis[18] and giant haemangiomas.[19]

Mechanical effects of IPC

The sudden application of a uniform external pressure on the lower extremity imposes a striking physiological change in the structure and haemodynamics of the lower extremity. If we focus on the deep veins there is a slow steady flow of blood within its lumen prior to compression. When compression is applied, the sudden pressure gradient at the compression zone accelerates the blood forward with a subsequent collapse of the lumen at the compression zone, effectively facilitating venous emptying and preventing stasis. The accelerated blood moves forward as a pulsatile volume that causes distention of the compliant lumen. This distention exerts up to a 20% strain on the endothelial cells when an external pressure of 50 mmHg is applied.[20] Moreover, if the pressure is applied sequentially, the accelerated blood flow could increase the peak flow velocity by over 200% within the lumen.[21] The higher flow velocity increases the shear stress on the endothelial cells lining the lumen, which may also facilitate clearance of the valve sinuses.

The different modality of external compression was studied using a computer-simulated model. It was found that a sequentially applied wavelike compression provides the most efficient method of venous emptying, suggesting that a sequential compression device may more efficacious in preventing DVT.[22]

IPC's effect of altering lower extremity hemodynamics is not limited to the venous system. By using venous plethysmography and heat flow calorimetry it could be demonstrated that venous pressure was lowered and blood flow was increased in the foot in subjects that received IPC.[23] The improved emptying of lower extremity veins and lowered venous pressure led to an increase in A–V pressure gradient. The increased disparity of A–V pressure also caused an increase in lower extremity arterial blood.[24] Furthermore, IPC has been reported to increase in the mean popliteal artery flow by as much as 93%.[25,26]

In a study of 40 lower limbs of 30 volunteers, the application of IPC was demonstrated to greatly enhance popliteal artery blood flow. It was postulated that the flow increase was due to a dramatic drop in the peripheral vascular resistance as the peak systolic and end diastolic flow velocities increase, and the reverse-flow component diminishes.[27] This increase in lower extremity arterial flow was not limited to healthy individuals. The increase in popliteal artery flow and foot skin perfusion occurred with patients with claudication as well as in those with occluded superficial femoral artery.[28] The increase in the A–V pressure gradient and subsequent increase in arterial flow caused by IPC has been postulated as a possible mechanism by which IPC improved patients with claudication.[15]

The circumferential compression of the lower extremity by IPC also transmits pressure to the subcutaneous tissues and the muscle groups. Compression increases the interstitial pressure in the extracellular space. When the interstitial pressure is greater than the hydrostatic pressure within the vessels, third spaced fluids are forced back into circulation. This phenomenon effectively decreases the cross-sectional area of the lower extremity and decreases the tensile stretch on the cutaneous tissues; especially in patients with an oedematous lower extremity. The decreased surface tension may provide improved transcutaneous oxygenation and clearance of metabolic toxins.[29]

However, the exact mechanism by which IPC aids in venous ulcer healing remains unclear. In a study of 10 patients with post-thrombotic leg ulcers, transcutaneous oxygen tension ($TcPO_2$) was higher after treatment with IPC (42.7 mmHg) compared to before treatment (26.2 mmHg). It was postulated that IPC decreased interstitial fluid volume and venous stasis, both of which lead to increased cutaneous tissue oxygenation.[29] However, other reports do not confirm this finding. Nemeth demonstrated that oedema removal by pneumatic compression did not alter $TcPO_2$.[30] In a study of 21 healthy adults and 23 elderly patients, another group found that $TcPO_2$ was decreased and $TcPCO_2$ increased during IPC.[31] The data suggests that the role of enhancement of cutaneous oxygenation and CO2 removal by IPC on wound healing is still unresolved.

Biochemical effects

A seminal observation was that when IPC was applied to the upper extremities, the incidence of DVT in the lower extremities could be lowered.[32] This finding suggested that IPC's efficacy in lowering the rate of DVT was not solely the direct result of mechanical

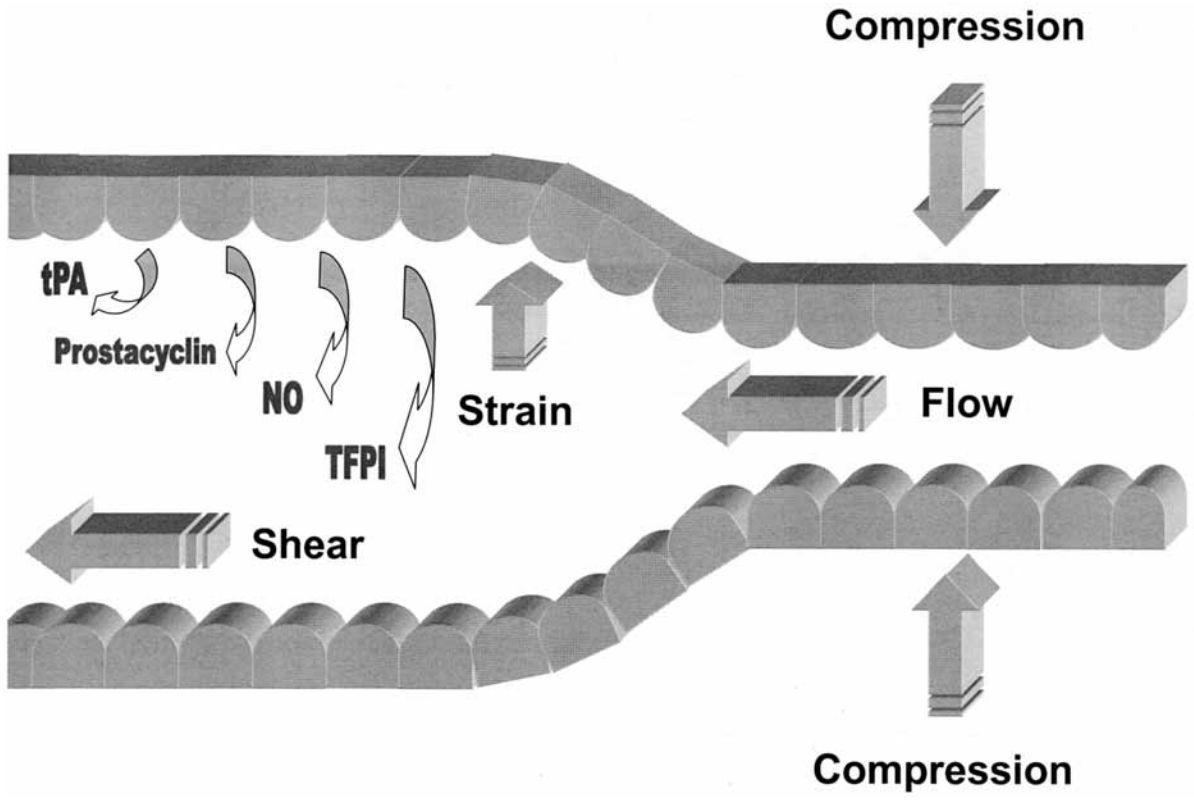


Fig. 1. Mechanical effects of pneumatic compression on a vein or artery. The pneumatic compression increases intravascular flow, shear and compressive strain on endothelial cells with the resulting release of biochemical mediators. tPA: tissue plasminogen activator; NO: nitric oxide; TFPI: tissue factor pathway inhibitor.

compression causing haemodynamic changes. Instead, the compressive forces of IPC also may have stimulated the systemic fibrinolytic capacity or other biochemical mechanisms of the circulation.

When IPC is applied to the lower extremity, the sudden compression causes a pulsatile flow to move forward while resulting in entirely draining of blood at the compression site. The distention caused by the rush of blood volume imposes a compressive strain on the venous endothelial cells, while the increased flow velocity imposes an increased shear stress on these same endothelial cells. This phenomenon also translates to the arterial system when the sudden decrease in the venous pressure causes an increase in the A–V pressure disparity leading to an increased arterial flow velocity. This effect increases shear stress on arterial endothelial cells. The mechanical forces of strain and shear have been shown in animal and cell culture models to cause physiological responses in endothelial cells that may contribute to the anti-thrombotic, pro-fibrinolytic, and vasodilatory effects of IPC (Fig. 1).

In vitro *studies of strain and shear and its clinical relevance to IPC*

Plasminogen is plasma glycoprotein made primarily in the liver, which when activated by agents such as tissue plaminogen activator (tPA), urokinase, streptokinase, tears, colostrum, or semen, becomes plasmin or fibrinolysin. It is known that plasminogen activator inhibitor (PAI) can inhibit this plasminogen activity. Plasminogens levels in plasma normally parallel fibrinogen levels and are increased after trauma and inflammation. tPA is produced by vascular endothelial cells (especially from venous sources).[33]

The application of cyclic strain >7% on cultured bovine endothelial cells induced a significant increase in immunoreactive tPA production. Moreover, immunocytochemical detection of intracellular tPA and mRNA expression of tPA significantly increased in endothelial cells subjected to more than 7% cyclic strain.[34,35] Cyclic strain also resulted in a 2.6-fold increase in the activity of the 1.4-kb tPA promoter after 4 h.[36] The frequency of the mechanical stretch in these

in vitro studies was set to approximate the heart rate (60 cycles/min), mimicking the strain caused by the beating heart on arterial endothelial cells. The relevance of these *in vitro* studies to IPC physiology remains speculative. Although IPC imposes strain on endothelial cells at a much lower frequency (1–2 cycles per minute), one could speculate that it may produce similar results. Nonetheless, these *in vitro* studies do provide a foundation for designing a model which more closely resembles the physiological environment created by IPC. Further research is needed to test these speculations.

When cultured endothelial cells are subjected to arterial shear stresses of 15 and 25 dynes/cm^2, the tPA secretion rate was 2.1 and 3.0 times greater, respectively, than the basal tPA secretion rate.[37] tPA mRNA levels were also increased greater than 10-fold when compared to stationary controls.[38] Although tPA mRNA expression was decreased to 10% of stationary control by low shear stress, tPA mRNA expression was increased over 250% at high shear stress in vascular smooth muscle cells.[39] Increased shear stress on vascular cells, though unproven, probably occurs when venous and arterial blood flow in the lower extremities increase secondary to IPC.

Whether or not the increased release of tPA by endothelial cells accounts for the therapeutic effects of IPC is still unclear. It has been postulated that fibrinolytic enhancement results in a decrease in the euglobulin lysis time.[40] Preoperative euglobulin lysis time was found to be a good predictor of the development of postoperative DVT. It was also noted that there is a decline in fibrinolytic activity in the immediate postoperative period.[41] IPC was found to reduce or even eliminate this decline in fibrinolytic activity.[42,43] After IPC was applied to the upper extremities, a similar increase in fibrinolytic activity was found, as suggested by a decreasing trend in euglobulin clot lysis time.[44] Many investigators have proposed that the increase in fibrinolytic activity was secondary to increase tPA release from endothelial cells.[43]

In an important study, Comerota and colleagues proposed a mechanism by which IPC increased fibrinolytic activity.[45] They studied six healthy volunteers and six post-thrombotic patients. After the subjects were exposed to IPC, their blood was drawn from an anticubital venous catheter. Fibrinolytic activity (euglobulin fraction, fibrin plate assay), tPA antigen and activity, plasminogen activator inhibitor-1 (PAI-1) antigen and activity and other components were assayed. In the six post-thrombotic patients, the baseline fibrinolytic activity was significantly less than that in the six healthy individuals. Moreover, it was not until the patients were stimulated by IPC that the patients' fibrinolytic activity levels reached the levels observed in normal individuals. These investigators also found a significant increase in fibrinolytic activity after 180 min of IPC exposure in normal subjects and in the postthrombotic patients. The tPA activity increased only in normal subjects, despite a decrease in tPA antigen, which occurred in both groups. Furthermore, the study found decreases in PAI-1 antigen and in PAI activity levels in both groups after IPC exposure. The investigators postulated that fibrinolytic activity was more critically related to the PAI-1 activity rather than the total amount of tPA present in circulation (as measured by tPA-antigen). Hence, it was the balance of PAI-1 activity, which was a function of total PAI-1 (PAI-1-antigen) and tPA-PAI-1 complexes in the circulation, and total free tPA-antigen that determined fibrinolytic capacity. IPC shifted this balance to favour increased fibrinolysis[45] (Fig. 2).

The effects of IPC on PAI-1 activity and total tPA in the circulation have also been studied. After obtaining femoral venous catheter blood samples, it was found that catheter placement caused elevation in PAI-1 and tPA-PAI complex, giving clues to why the presence of intravenous catheters are prothrombotic. However, IPC induced significant increases in fibrinogen degradation products, and fibrin degradation products, but decreased euglobulin lysis time. Furthermore, IPC had no definitive effect on total tPA levels in the circulation. It was proposed that perhaps the increased tPA is complexed with PAI-1 leading to an increase in the level of tPA-PAI-1 complexes. The data also showed a decrease in total PAI-1, suggesting that the decrease may be secondary to increase consumption of PAI-1 from increase tPA secretion by endothelial cells after IPC exposure.[46]

However, these findings did not go unchallenged. In a study of 21 healthy individuals, euglobulin lysis time, tPA antigen, PAI-1 antigen, and PAI-1 activity measurements showed that IPC did not cause any statistically significant changes in any of parameters used to measure fibrinolysis. The authors noted that circadian rhythm seemed to have more influence on fibrinolysis than IPC.[47] This finding was confirmed by another study of 10 healthy volunteers which found that although increases in venous flow velocity were seen in the common femoral vein, no changes in tPA or PAI-1 antigens were observed with IPC.[48] In a recent study of 48 patients undergoing abdominal surgical procedures, the effects of IPC, and heparin injections on systemic fibrinolysis were compared. This was done by measuring tPA and PAI-1 by amidolytic methods.

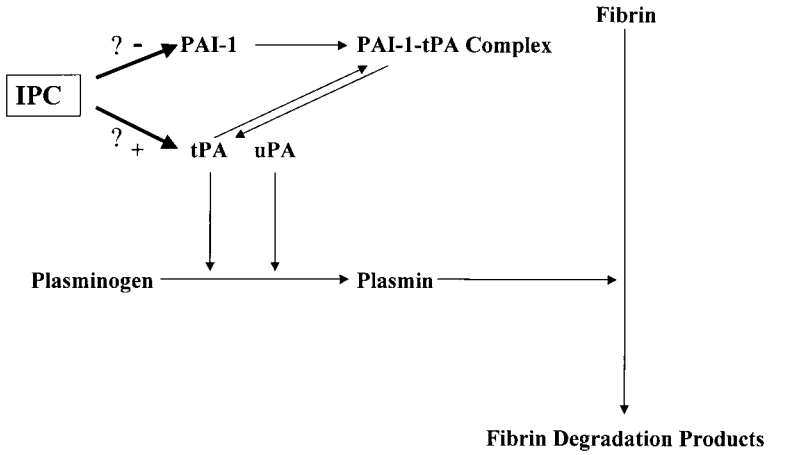


Fig. 2. Possible mechanical effects of intermittent pneumatic compression on fibrinolysis. IPC: intermittent pneumatic compression; PAI: plasminogen activator inhibitor; tPA: tissue plasminogen activator; uPA: urokinase plasminogen activator.

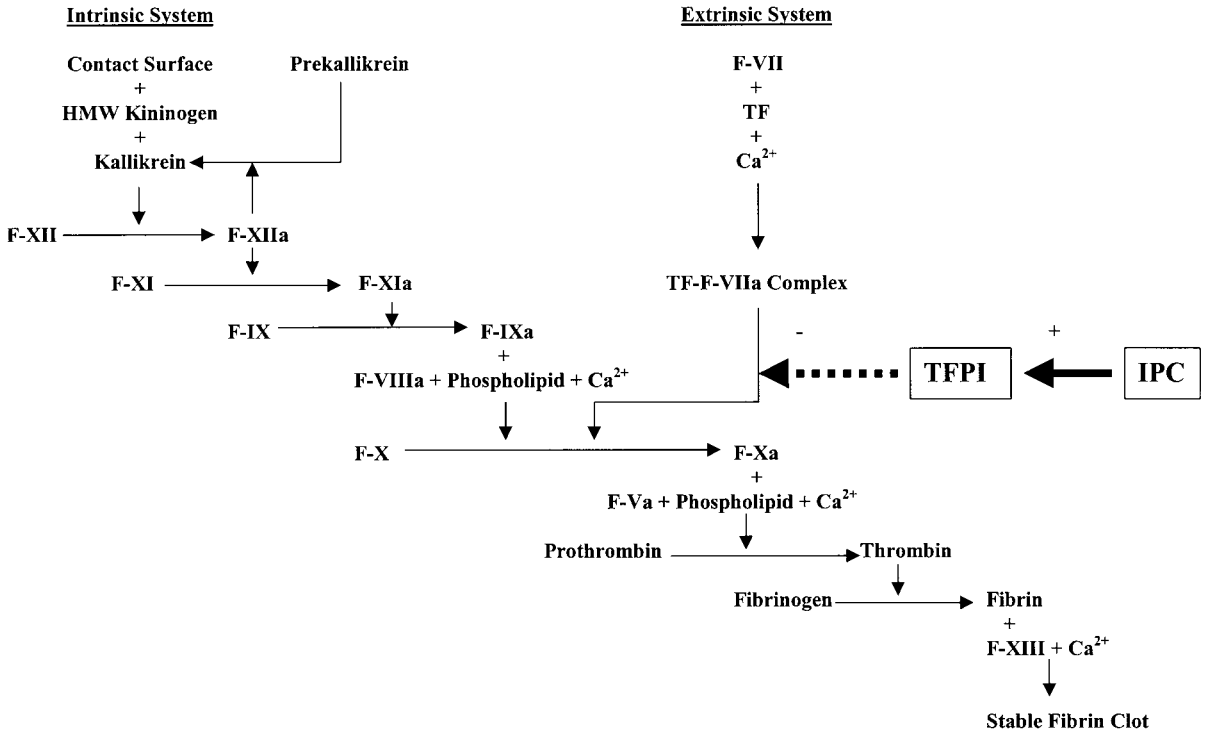
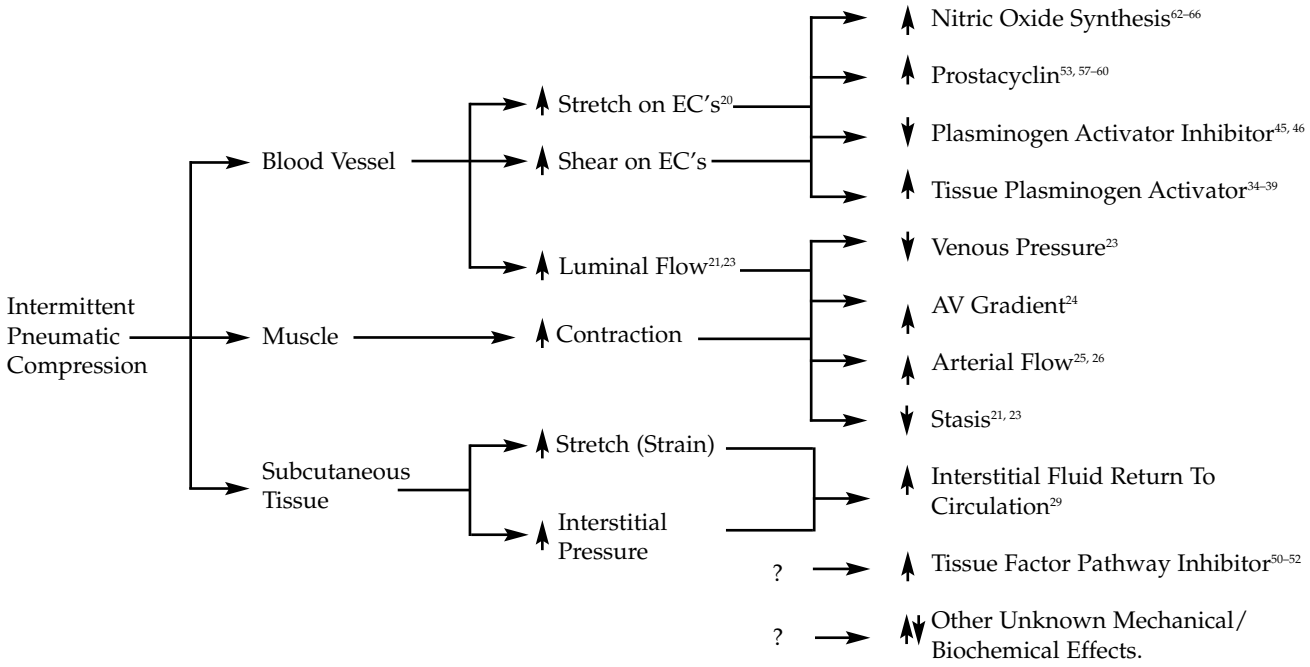


Fig. 3. Mechanical effects of intermittent pneumatic compression on the coagulation pathway. HMW: high molecular weight; TF: tissue factor; F: factor; TFPI: tissue factor pathway inhibitor; IPC: intermittent pneumatic compression.

Although the study was able to show that postoperative reduction in fibrinolytic activity did occur, there were no appreciable changes in tPA activity or PAI-1 activity. The authors concluded that IPC had no effect on the postoperative decrease in fibrinolytic activity and that its therapeutic effect on DVT prophylaxis was purely a result of altered haemodynamics that reduced lower extremity venous stasis.[49] These conflicting data suggest further study is needed to resolve the issue of whether IPC affects systemic fibrinolysis.

The importance of a tissue factor pathway inhibitor as an important regulator of the initiating event in blood coagulation in the extrinsic coagulation system or the tissue factor pathway has also been recently appreciated.[50] When factor VIIa (activated form of factor VII) is complexed with tissue factor (TF), it will activate factor X and IX, ultimately leading to the

Table 2. Mechanical effects of intermittent pneumatic compression.



activation of prothrombin and subsequently thrombin, culminating in coagulation. Tissue factor pathway inhibitor directly inhibits factor Xa and the TF-factor VIIa complex.[50] Since heparin elevates tissue factor pathway inhibitor, its anticoagulating effect may at least partly be the result of the physiological effect of tissue factor pathway inhibitor on the extrinsic coagulation system.[51]

Another antithrombotic mechanism of IPC has been proposed. In a study of six healthy individuals and six patients with post-thrombotic venous disease, the investigators found that after exposing the individuals to IPC for 180 min there was a significant increase in the plasma tissue factor pathway inhibitor levels in both groups. Moreover, there was also a significant decrease in the level of activated factor VII (VIIa) in both groups and an inverse relationship between the level of tissue pathway inhibitor and factor VIIa. It has been postulated that the increase in tissue factor pathway inhibitor after IPC exposure was likely a result of increased release of the inhibitor from within endothelial cells or from the cellular surface.[52] This form of issue factor pathway inhibitor is more effective in anticoagulation than the truncated inhibitors bound to lipoprotein in plasma.[53] The increase in tissue factor pathway inhibitor and the concomitant decrease in factor VIIa levels are likely to be contributing factors by which IPC prevents venous thrombosis[52] (Fig. 3).

Another pathway by which IPC works may be in its impact on platelet aggregation. Prostacyclin, an endothelial released autacoid, is the most potent endogenous inhibitor of platelet aggregation known. It stimulates platelet disaggregation, and is a potent inhibitor of smooth muscle cell contractions causing vasodilatation. Prostacyclin elevates levels of adenyl cyclase with an increase in cAMP, decreasing ionised calcium and inhibiting aggregation.[54,55] It also increases red blood cell deformity, to facilitate blood flow in vasculature with high resistance.[33] Prostacyclin also has a pro-fibrinolytic effect as demonstrated by a study which found increased levels of tPA activity with shortened euglobulin clot lysis time in patients treated with prostacyclin and iloprost (a stable analogue of prostacyclin) infusions.[56]

After exposing cultured endothelial cells to cyclic strain of 24% at cycles of 10 s of elongation followed by 10 s of relaxation, the prostacyclin synthetic capacity increased in a time-dependent manner.[57] Prostacyclin release was also enhanced in endothelial cells subjected to elevated shear stress.[58,59] When intact human umbilical vein conduits were subjected to 25 dyn/cm^2, there was upregulation of prostacyclin synthase after 6 h and an increased accumulation of alpha 6-keto prostaglandin, the stable metabolite of prostacyclin, in the perfusion medium.[60] These *in vitro* data are supported by a clinical study. In a prospective study of 26 patients undergoing surgery, there was an elevation in the level of 6-Keto-prostaglandin-F1a in the

femoral vein plasma when obtained from an extremity undergoing external IPC.[61]

Vasodilation is another possible mechanism by which IPC improves perfusion in patients with arterial occlusive disease. Endothelial cells produce an endothelium-derived relaxing factor identified as nitric oxide. Like prostacyclin, nitric oxide is a potent inhibitor of smooth muscle cell contractions, which causes vasodilation. Nitric oxide also inhibits platelet aggregation, stimulates disaggregation, inhibits platelet and monocyte adhesion to endothelial surfaces, and inhibits smooth muscle cell proliferation. Nitric oxide is released following vascular injury by mechanical or biochemical stimuli. Its production however, is markedly diminished following reperfusion of ischaemia.[62]

Studies have shown that when cultured endothelial cells were exposed to shear mechanical stress (lamina flow at 16 to 20 dynes per cm^2), endothelial nitric oxide synthase mRNA is up-regulated.[63] Increased shear on the superior mesenteric artery of rats also increased nitric oxide synthesis.[64,65] Moreover, when cultured endothelial cells were subjected to 24% cyclic strain, at 60 cycles/min, they exhibited significant increased endothelial nitric oxide synthase activity when compared with stationary controls.[66]

In a study of 80 male rats, vasodilation was maximal by 30 min after initiation of IPC. This vasodilation was completely blocked by an inhibitor of nitric oxide (NG-monomethyl-L-arginine), implying a positive role of nitric oxide. Inflation rate played an important role in the modulation of distant microcirculation induced by IPC while peak-pressure duration did not. The shortest inflation rate of 0.5 s induces the greatest vasodilation. Assuming that a shorter inflation rate creates a faster peak flow velocity, the data are consistent with the hypothesis that increased shear stress on the vascular wall stimulates vascular endothelium to release NO causing vasodilation.[67]

Summary

Table 2 summarises the current understanding of the mechanism by which IPC works. Although there are many *in vitro* studies that show the effects of strain and shear on endothelial cells, it is by no means conclusive that those studies necessarily predict the effects of IPC *in vivo*. The *in vitro* studies were conducted in conditions and environments that were analogous but not synonymous with the effects of mechanical IPC. Moreover, the exact amount of mechanical shear and strain imposed on venous or arterial endothelial cells by IPC *in vivo* are unknown. The *in vitro* studies do provide an attractive model to test the postulate that the mechanoreceptors in endothelial cells, when activated, lead to a myriad of biochemical processes consisting of enhanced fibrinolysis, platelet disaggregation, and vasodilatation. Currently, an *in vivo* model that could accurately mimic the physiological effects of IPC in humans is still lacking. Until such a model is incorporated into new experimental designs, definitive answers to the mechanistic actions of IPC cannot be fully addressed. Nonetheless, the clinical studies do support the notion that IPC's effects are not purely mechanical and that the release of biochemical mediators may play a role that is at least as important. The reviewed studies provide strong foundations on which further studies could be designed to accurately predict the mechanical outcome of IPC and its biochemical consequences.

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