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Intermittent pneumatic compression: Physiologic and clinical basis to improve management of venous leg ulcers

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Venous leg ulcers (VLUs) are a significant health problem that afflicts 1% of the population at some point during their lifetime. Intermittent pneumatic compression (IPC) is widely used to prevent deep venous thrombosis. However, IPC seems to have application to a broader base of circulatory diseases. The intermittent nature of pulsatile external compression produces beneficial physiologic changes, which include hematologic, hemodynamic, and endothelial effects, which should promote healing of VLUs. Clinical studies of the management of VLUs show that IPC increases overall healing and accelerates the rate of healing, leading to current guideline recommendations for care of patients with VLUs. Proper prescription of IPC to improve the management of patients with VLUs requires further definition. It seems that application of IPC in combination with sustained graduated compression improves outcome in patients with the most advanced venous disease. (J Vasc Surg 2011;53:1121-9.)

Intermittent pneumatic compression (IPC) is an effective treatment for a variety of circulatory disorders. Its use for venous thromboembolism prophylaxis and treatment of lymphedema are well established.[1] IPC also improves walking distance in patients with intermittent claudication and is effective in patients with critical limb ischemia (CLI). However, the focus of this discussion will be the utility of IPC for the management of advanced chronic venous disease, specifically venous ulceration.[1]

Venous leg ulcers (VLUs) impose a major healthcare burden on the patient and the healthcare system. The direct and indirect costs of chronic venous disease (CVD) have been estimated at one billion U.S. dollars per annum.[2] This review addresses the etiology of VLUs, the importance of compression in their management, the hemodynamic and hematologic effects of IPC, and the clinical outcomes observed when IPC is used to treat VLUs.

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CAUSES OF VENOUS LEG ULCERS

VLUs occur in approximately 1% to 2% of the population.[3-5] The underlying pathophysiology is ambulatory venous hypertension resulting from valvular incompetence, obstruction of the vein lumen, or both. Valve incompetence can result from a primary defect in the vein wall or be secondary to the inflammatory and fibrotic sequelae of venous thrombosis. Acute deep venous thrombosis (DVT) can obstruct the vein, subsequently causing valvular dysfunction in nonthrombosed distal veins, and impair calf muscle pump function. Prolonged immobility and obesity also result in calf muscle pump dysfunction, venous pooling, and chronic edema. Valvular dysfunction can occur when individuals with a genetic predisposition for venous insufficiency are exposed to risk factors, such as pregnancy or periods of prolonged standing. Regardless of its etiology, however, the ensuing venous stasis, which is characterized by the formation of edema and a rise in tissue pressure, plays a major role in the development of venous ulcers.

PATHOPHYSIOLOGY OF VENOUS LEG ULCERS

Two important hemodynamic pumps (the calf and foot pumps) propel blood proximately from their respective venous reservoirs. Contraction of calf muscles activates the calf pump, which drains blood from both calf and foot, whereas pressure on the plantar arch (during ambulation) empties blood from the plantar venous plexus through the lateral plantar vein. Ineffective leg pumps, together with incompetent venous valves, lead to elevated tissue pressure

and edema. Individuals with associated venous obstruction have the highest ambulatory venous pressure. Venous hypertension increases capillary permeability, and the resulting blood and fluid leakage into tissue causes edema, pigmentation, and tissue fibrosis.[6,7]

The mechanism by which prolonged venous hypertension causes venous ulcers is the subject of several theories. Browse and Burnand[8] suggested that venous hypertension resulted in a distended capillary bed and enlarged endothelial pores, allowing fibrinogen to escape into the interstitial fluid. They proposed a "fibrin-cuff" hypothesis based on their observation that pericapillary fibrin formed a "cuff" around an enlarged dermal capillary bed, with the fibrin acting as a barrier to tissue oxygenation, causing hypoxia-induced ulceration.

The "fibrin-cuff" hypothesis has been superseded by more recent theories, indicating that chronic inflammation plays a crucial role in the progression of CVD.[9] Although the precise events that initiate this inflammatory response are not known, it seems to involve leukocyte-endothelial interactions triggered by abnormal venous return and venous hypertension.[9] Prolonged pooling of venous blood distends the vein and distorts venous valves, allowing leakage through the valves. This pooling creates a region of low flow and zero-shear stress. The resultant venous hypertension, leukocyte activation, and adhesion to and emigration through the venous endothelium trigger inflammatory reactions, further increasing capillary permeability.[10,11]

Regardless of its etiology, however, prolonged venous hypertension initiates the progression of a series of pathologic events, causing effects at a cellular level and resulting in the clinical signs and symptoms of CVD, which can ultimately result in skin breakdown and ulceration.

SUSTAINED COMPRESSION: THE CORNERSTONE OF VENOUS LEG ULCER TREATMENT

Sustained compression is the cornerstone of VLU therapy, the goal of which is to promote ulcer healing and prevent recurrence. However, the healing of venous ulcers, especially those that are large and longstanding, may not occur, even after many months of treatment.[10] Several randomized studies have shown that only 37% to 55% of ulcers heal completely after 12 weeks of compression therapy.[11-13] The VenUS I trial, which randomized two types of compression bandages for treating VLUs in 387 patients, found that 37% healed with short-stretch bandages at 12 weeks vs 46% treated with four-component, multilayer bandages.[11] The respective healing rates at 24 weeks were 68% and 55% ($P = .05$). Short-stretch bandages retain some elasticity, whereas four-component, multilayer bandages are essentially inelastic and apply persistent pressure to the limb, more when the patient is upright, less when supine. In a trial of 200 patients with VLUs randomized to treatment with either four-component bandages or usual care (control group), O'Brien et al[12] reported that the healing rate at 3 months was 54% with four-component bandages vs 34% with usual care ($P < .001$). However, only 5 patients in the "usual care" group received compression, which seems to be a common scenario in many medical communities. Lyon et al[13] treated 165 patients with chronic venous ulcers with a hydrocolloid dressing and application of an Unna boot. Healing was achieved in 55% by 12 weeks. A subsequent analysis of the data by Phillips et al[14] suggested that ulcers that are large, longstanding, and slow to heal after 3 weeks of optimal therapy are unlikely to resolve rapidly and may benefit from alternative treatments.

Tinkler et al[5] found that 34% of ulcers treated with three-component bandages and 32% of those treated with four-component bandages healed by 12 weeks. Because the degree of compression was likely similar with the two bandaging techniques, similar results would be anticipated.

PHYSIOLOGIC EFFECTS OF INTERMITTENT PNEUMATIC COMPRESSION

Table I summarizes the hemodynamic and hematologic effects of IPC.

Hemodynamic effects. Sustained compression applied by multilayer bandages reduces venous hypertension; however, it only passively promotes venous return compared to IPC.[9] IPC actively compresses the leg, mimicking the action of the leg muscle pumps. The device, which may have one or more chambers, consists of a pneumatic pump that inflates air into garments wrapped around the foot, calf, thigh, or combinations thereof. Devices with multiple chambers can provide sequential compression in an ascending pattern up the limb. Pumps vary in their timing cycle and amount of pressure produced, ranging from low-pressure, slow-inflation to high-pressure, and rapid-inflation devices.

IPC reduces venous stasis and increases flow velocity in the deep veins, resulting in favorable hemodynamic changes such as decreased venous pressure and interstitial edema.[1,7] IPC produces increases in venous volume flow and increased venous flow velocity, causing increased shear stress.[15] Research studies in animals have shown that these mechanical forces result in endothelial cell responses that contribute to the profibrinolytic, vasodilatory, and antithrombotic effects of IPC.[1]

Malone et al[16] compared the effects of high-pressure, rapid-inflation IPC vs low-pressure, slow-inflation IPC on 11 healthy subjects and 11 patients with postthrombotic venous disease. Although both systems increased the velocity in femoral and popliteal veins in all study participants, the high-pressure, rapid-inflation devices produced the highest peak velocities ($P < .05$). All venous velocities, both baseline and stimulated by IPC, were significantly attenuated in postthrombotic patients.

Hematologic effects. The mechanisms by which IPC induces hematologic alterations has been studied and clarified. Changes in blood coagulation are attributed to increased shear stress on the vein wall. This is consistent with the results of studies in cell culture models showing that increasing shear stress on endothelial cells increases production of prostacyclin, endothelial-derived relaxing factor, platelet-derived growth factor, and tissue-type plasminogen activator.[17-20]

Table I. Physiologic effects of IPC

Category	*Physiologic effect*[1,10,18]	*Potential direct and indirect benefits*[1,10,24-25,28]
Hemodynamic/ hematologic	↓ Venous stasis ↑ Flow velocity in deep veins ↑ Fibrinolysis ↑ Blood volume flow ↑ Endothelial shear stress ↓ A-V pressure gradient ↑ Shear stress/on endothelial strain cells	↓ Venous pressure ↑ Interstitial edema ↑ Thrombogenicity ↑ Intravascular coagulation ↑ Venous emptying ↓ Stasis ↓ Edema ↑ Arterial inflow ↑ Fibrinolysis ↑ Vasodilation ↓ Thrombosis

Category	*Physiologic effect*[24-25]	*Potential direct and indirect benefits*[20-22.24-25]
Hemodynamic/ hematologic (cont'd)		↑ Prostacyclin production ↓ Endothelial-derived relaxing factor ↓ Platelet-derived growth factor
Fibrinolytic/ hematologic	↑ Fibrinolytic activity ↓ tPA antigen ↑ tPA activity ↓ PAI-1 antigen ↓ PAI-1 activity ↓ FVIIa levels ↑ TFPI levels	↑ Endogenous fibrinolytic activity ↑ Thrombosis ↓ Intravascular coagulation ↓ Hypercoagulability

Category	*Physiologic effect*[26-28]	*Potential direct and indirect benefits*[26,28]
Tissue oxygen tension	↑ $TcPO_2$ levels ↓ Interstitial fluid volume ↓ Venous stasis	↑ Oxygen diffusion barrier ↓ Leg edema ↑ Skin temperature
Edema	↓ Arteriovenous shunting ↓ Edema	↑ Capillary perfusion ↑ Skin nutrition

A-V, Arterio-venous; *FVIIa*, factor; *IPC*, intermittent pneumatic compression; *PAI-1*, plasminogen activator inhibitor-1; *$TcPO_2$*, transcutaneous oxygen tension; *TFPI*, tissue factor pathway inhibitor; *tPA*, tissue plasminogen activator; *VIIa*.

IPC alters fibrinolytic activity and seems to affect two of the three limbs of Virchow's triad: stasis and hypercoagulability. Endogenous fibrinolysis results from the conversion of plasminogen to plasmin through the action of one of two activators, tissue-type plasminogen activator (tPA) and/or urokinase-type plasminogen activator (uPA). Lytic activity is neutralized when plasminogen activator is bound by circulating plasminogen activator inhibitor-1 (PAI-1) and when plasmin is bound by α-2-antiplasmin.

Comerota et al[21] proposed the mechanism by which IPC increases fibrinolytic activity based on the results of a controlled study evaluating normal subjects and patients with post-thrombotic CVD. Fibrinolytic activity was assessed using a calibrated fibrin-plate assay, which assesses total fibrinolytic activity in the blood. Also studied were tPA and PAI-1 antigen and activity, plasmin generation, and von Willebrand factor (vWF) as a gauge of endothelial stimulation. Interestingly, but not surprisingly, baseline endogenous fibrinolytic activity was significantly attenuated in postthrombotic patients ($P < .01$). IPC increased endogenous fibrinolytic activity in all patients. However, the increase of fibrinolytic activity of postthrombotic patients was attenuated, essentially reaching baseline levels observed in healthy patients. Interestingly, IPC reduced tPA antigen, whereas tPA activity significantly increased tPA activity. IPC reduced PAI-1 antigen and activity; however, there was no change in vWF. These observations suggest that the increase in fibrinolytic activity is due to a reduction in PAI-1, most likely resulting from increased clearance. Unlike cell culture studies, there was no increase in the release of tPA from endothelial cells.

Extending the findings of Comerota et al,[21] Chouhan et al[22] examined the onset of intravascular coagulation through the tissue factor (TF) pathway. IPC reduced factor VIIa (FVIIa) levels for both healthy patients and postthrombotic patients compared with their baseline values ($P < .001$). There was a greater ($P < .05$) decrease in FVIIa levels in healthy patients (18% to 24% of baseline values) than in patients with postthrombotic venous disease (40% to 43% of baseline values). Likewise, there was a greater increase in tissue factor pathway inhibitor (TFPI) levels in healthy patients than in post-thrombotic patients ($P < .001$). An inverse relationship was found between FVIIa and TFPI levels, demonstrating inhibition of the TF-dependent pathway.

These findings suggest that IPC stimulates the release of TFPI from the endothelial TFPI pool and indicate that reduction of intravascular coagulation through inhibition of the TF pathway may be a key mechanism for the antithrombotic effect of IPC.

Effects on oxygen tension. When edema occurs and increases extravascular pressure, perfusion pressure decreases, reducing dermal oxygen tension. Kolari et al[23] postulated that IPC would increase transcutaneous oxygen tension ($TcPO_2$) and contribute to ulcer healing by decreasing interstitial fluid volume and venous stasis. They compared the effect of IPC in 10 patients with postthrombotic leg ulcers and 9 healthy patients and found that $TcPO_2$ increased in 9 of 10 patients. Baseline $TcPO_2$ was greater in healthy patients ($P < .01$) than in patients with leg ulcers, both before and after IPC. The change in $TcPO_2$ of patients directly correlated with a reduction of leg edema and inversely correlated with skin temperature ($P < .002$).[3] These results support the hypothesis that an oxygen diffusion barrier is present in the tissue surrounding venous ulcers and suggest that IPC increases tissue perfusion and decreases interstitial fluid volume in the leg, resulting in improved oxygen diffusion.

A subsequent study by Nemeth et al[24] in patients with venous ulcers and pitting edema failed to show an increase of $TcPO_2$ with IPC. Nemeth et al[24] and Kolari et al[23] used different devices, with markedly different inflation times and cycles. The cycle times in the Kolari et al[23] study were 30 seconds (12-second inflation, 18-second deflation) compared to 120 seconds (90-second inflation, 30-second deflation) in the Nemeth et al[24] study. Because normal venous refill times are 25 seconds or less, it is understandable that a 30-second cycle time (two compressions/minute) would be superior to a 120-second cycle time (one compression every 2 minutes). The shorter cycle time maximizes endothelial shear stress and emptying of venous blood from the leg.

Effects on edema. A number of studies have shown that IPC reduced edema in patients with CVD and VLUs. Malanin et al[25] investigated the hemodynamic and volumetric effects of IPC in patients with VLUs and recorded tibial artery Doppler scan waveforms and skin perfusion with laser Doppler flux. IPC produced a significant reduction in leg volume in patients with VLUs compared to healthy patients ($P = .016$). The authors suggested that reduction of edema leads to a redistribution and increase of skin blood flow favoring superficial capillary perfusion.

Effects of intermittent pneumatic compression on arterial perfusion. Emptying of the venous blood from larger veins and venules of the leg increases the arterial-venous pressure gradient. By taking advantage of this principle, IPC was studied as a method to improve arterial blood flow.[26-40] Early investigation using massage pumps on the lower extremity of individuals in the upright position demonstrated reduced venous pressures.[26] The pressure in arteries of the dependent lower extremity will increase by an amount corresponding to their distance below the heart. An arterial-venous pressure differential of 30 to 40 mm Hg or more can be produced with IPC resulting in an increased perfusion pressure, which naturally leads to an increase of total blood flow to the part of the extremity being compressed. As early as 1957, Allwood[41] demonstrated that intermittent leg compression in the normal individual could increase blood flow by 60% and by 30% in patients with arterial occlusive disease.

Henry and Winsor[26] also demonstrated increased foot perfusion when they recorded rapid clearance of I-131 from tissues of the foot because of calf compression. Venous pressure and tissue pressure were reduced and oxygen tension in blood from the veins of the dorsum of the foot was increased. The authors speculated that if the foot and calf were compressed, lower venous pressures and higher arterial-venous pressure gradients would be achieved than with calf compression alone, with a corresponding improvement in foot perfusion.

Eze et al[42] studied the influence of combined foot and calf compression on foot skin perfusion and popliteal artery blood flow in normal volunteers and claudicants with superficial femoral artery occlusion. High-pressure (120 mm Hg), rapid-inflation (0.3 seconds) compression was used at two cycles/minute. Skin blood flow to the great toe increased by 328% in control patients and 188% in claudicants, whereas popliteal artery blood flow increased by 173% and 50% in controls and claudicants, respectively. They found that foot skin perfusion was optimized with foot compression alone, whereas optimal popliteal artery blood flow was observed with combined foot and calf compression. These authors went on to characterize the source of improved foot skin perfusion that potentially could be from increased arterial inflow or venous reflux resulting from proximal compression. They found that 86% to 93% of the increased foot skin perfusion was due to improved arterial flow and 7% to 14% due to venous reflux. Greater venous reflux was observed in individuals who exercised (perhaps reflecting peripheral vasodilation), whereas lesser reflux was observed in sedentary patients.

Investigators have used IPC to treat patients with intermittent claudication and CLI.[31-40] Randomized trials of IPC in patients with intermittent claudication have demonstrated improved walking distances associated with an increase in their ankle-brachial index.

The degree of improved arterial perfusion is reduced in patients with occlusive disease. However, substantial increases in blood flow and foot skin perfusion have been documented in patients with CLI. The number of patients treated with IPC for CLI is limited and the studies are not well controlled. However, investigators have reported better than anticipated outcomes in patients with end-stage CLI who had no options for revascularization.[34,39,40]

Because patients with venous leg ulcers have reduced nutritional blood flow to the skin and reduced $TcPO_2$[23], improved arterial perfusion to the limb and improved skin perfusion represent additional and important mechanisms by which patients with venous ulcers benefit from IPC.

USE OF INTERMITTENT PNEUMATIC COMPRESSION IN PATIENTS WITH VENOUS LEG ULCERS

Ever since McCulloch[43] suggested the use of IPC for the treatment of venous ulcers in 1981, evidence has been accumulating supporting IPC as an adjunctive method to speed the healing of venous ulcers (Table II). This review only includes studies that report 10 or more patients. In 1981, Hazarika and Wright[44] reported a prospective, controlled trial evaluating the effects of a single-chamber IPC device on ulcer healing in 21 patients with VLUs. Nine patients received IPC treatment and 12 served as controls. IPC patients were allowed to select their pressure settings (30-80 mm Hg) and were instructed how to use the device at home for 2 to 3 hours daily. All but 1 of the IPC patients exhibited subjective and/or objective healing of their ulcers after 10 to 40 weeks of IPC treatment, whereas 11 of the 12 control patients showed no change or worsening of their condition. Importantly, it was the patients with the most severe and longstanding ulcers that showed improved ulcer healing with IPC.

In a prospective, randomized, controlled study, McCulloch et al[45] examined the effects of single-chamber IPC on rates of venous ulcer healing. All 22 patients enrolled in

Table II. Use of IPC in the treatment of VLUs: study summary

Investigator	*Study design*	*No. patients*	*IPC protocol*	*Duration*	*Results*	*Comments*
Hazarika and Wright[44]	Prospective, controlled trial. All patients previously treated with compression bandages and topical agents. Outpatient study.	21	2-3 h/d IPC with a single-chamber sleeve. Inflation to 30-80 mm Hg × 120 s, followed by 135 s deflation.	44 wks	8/9 (89%) test subjects improved; 11/12 (92%) control subjects no change or worsening.	Case series; no ITT analysis; inconsistent compliance.
McCulloch et al[45]	Randomized; controlled; 12 IPC + Unna boot vs 10 Unna boot alone. Outpatient study.	22	Single-chamber IPC 1 h 2×/wk at 50 mm Hg × 90 s, followed by 30 s deflation.	6 mo	Ulcer healing: 12/12 – IPC 8/10 – control Healing rate: 0.15 cm^2/d – IPC 0.06 cm^2 – control (P = .05).	Control patients were older. Unclear whether initial ulcer size was comparable between groups.
Smith et al[46]	Randomized; 21 patients to wound care, stockings plus IPC; 23 patients to wound care, stockings; controlled; 'intention to treat' analysis. Ulcers present <12 wks. Outpatient setting.	45	All subjects received 30-40 mm Hg graduated compression stockings and routine wound care. Sequential IPC applied up to 4 h/d: Ankle – 50 mm Hg Calf – 45 mm Hg Thigh – 40 mm Hg	3 mo	Ulcer healing: 10/21 – IPC 1/23 – control P = 0 Healing rate (surface area/wk): 19.8% – IPC 2.1% – control (P = .046).	Well-controlled trial. IPC applied over compression stocking. IPC cycle time not specified.
Mulder et al[47]	Open-label cohort study; historical controls; chronic (<1 y) venous ulcers. All patients had no improvement after 42 d of Unna's boot.	10	Sequential IPC × 1 h in the AM and 2 h in the PM: Ankle – 50 mm Hg Calf – 45 mm Hg Thigh – 40 mm Hg	1 y	All patients improved (P < .01); 1 patient healed by 4 mo. All patients healed by 1 y.	Small sample size; IPC cycle times not specified.
Schuler et al[48]	Randomized comparison. IPC + 30 mm Hg elastic stocking vs Unna's boot. Outpatient setting.	54	IPC patients given 30 mm Hg elastic stocking. Graduated compression IPC × 1 h in the AM and 2 h in the PM: Foot – 10 mm Hg Calf to ankle – 50, 45, 40 mm Hg at 2.5 s intervals. 12 s compression; 60 s deflation.	6 mo	Ulcer healing: 20/28 – IPC + stocking. 15/25 – Unna's boot. Healing rates similar and correlated with pretreatment ulcer size. Less pain (P < .03) and exudate (P < .05) in IPC group.	Effects of IPC not evaluated in a controlled setting. The 30 mm Hg stocking was probably less effective than the Unna's boot for leg ulcer treatment.

Table II. Continued

Investigator	*Study design*	*No. patients*	*IPC protocol*	*Duration*	*Results*	*Comments*
Alpagut and Dayioglu[49]	Prospective, non-randomized trial of 159 patients with post-thrombotic venous ulcers given routine care of: leg elevation, compression with elastic stockings, oral and IV anticoagulants, and systemic antibiotics. 76 received IPC in addition to compression stockings. Inpatient and outpatient setting.	235	1 h/d of single-chamber IPC at 70 mm Hg pressure. 1 min cycles: 20 s of inflation, 20 s of sustained compression, and 20 s of deflation.	3 mo	Time to heal: 20 d – IPC 90 d – control Return to activity: 7 days – IPC 25 days – control	Study not randomized; initial ulcer size not documented; no statistical analysis performed. 1 hr/day IPC seems minimal
Nikolovska et al[50]	Randomized trial (1:1) in patients with venous ulcers. Rapid inflation/short cycle vs slow inflation/long cycle IPC. Routine care of hydrocolloid dressings for all, with no other compression. Inpatient and outpatient setting.	104	1 h/d compression: 45 mm Hg ankle, 35 mm Hg calf + ankle; 30 mm Hg thigh in both groups. Rapid inflation: 0.5 s inflation, 6 s sustained compression, 12 s deflation. Slow inflation: 60 s inflation, 30 s sustained compression, 90 s deflation.	6 mo or until complete ulcer healing.	Ulcer healing: 45/52 – rapid IPC 32/52 – slow IPC (P = .004) Healing rate: 0.09 cm^2 – rapid IPC 0.04 cm^2 – slow IPC (P = .0002).	First study comparing 2 different IPC compression cycles. Only patients with pure venous ulcers were enrolled.

d, Day; *h/d*, hours/day; *h*, hour; *IPC*, intermittent pneumatic compression; *ITT*, intent-to-treat; *IV*, intravenous; *mo*, month; *s*, seconds; *VLU*, venous leg ulcer.

this trial received local wound care and application of an Unna boot. Twelve patients were randomized to IPC treatment twice weekly for 1 hour per session. Follow-up visits were conducted twice weekly for 6 months or until the ulcers healed. Results showed that ulcer healing occurred in all 12 of the patients who received IPC and in 8 of 10 control patients. Ulcer healing rate was more rapid in patients receiving IPC (0.15 cm^2 per day) compared to patients in the control group (0.08 cm^2 per day; P = .05). It is interesting that benefit from IPC (speed of healing) was observed in light of what most would consider minimal use of IPC. Because edema occurs on a daily basis and is worse in the later hours of the day, longer durations of IPC delivered on a daily basis would mitigate the effects of venous hypertension, increasing the likelihood of salutary outcomes.

In a well-designed study, IPC was applied over 30 to 40 mm Hg elastic compression stockings in patients with venous ulcers.[46] Patients were randomly assigned to one of two groups: compression stockings and routine wound care (N = 24) or compression stockings, routine wound care, and adjunctive home-based IPC for 3 months or until ulcer healing (N = 21). IPC was used 3 to 4 hours per day. By week 12, 48% of the IPC group had complete ulcer healing vs 11% in the stocking alone group (P = .009). The median ulcer healing rate for the IPC group was 19.8% area per week vs 2.1% in the control group (P = .046).

Using patients as their own control, Mulder et al[47] studied the effect of a sequential compression device on 10 patients with chronic venous ulcers who failed to improve after 42 days of therapy with an Unna boot and elastic wrap. Patients were instructed to use the IPC device for 1 hour in

the morning and 2 hours each evening, targeting healing at 120 days of treatment. Although only 1 patient healed by the 120-day time point, all showed marked improvement. Continued treatment resulted in complete healing of all but 1 patient.

In a study conducted by Schuler et al,[48] 53 patients with chronic venous ulcers were randomly assigned to receive either an Unna boot or sequential IPC with an elastic stocking delivering 30 mm Hg compression at the ankle. The stocking was worn all day, except during application of the device. Follow-up was conducted once weekly for 6 months or until ulcer healing was complete. Complete ulcer healing was achieved in 15 of 25 patients (60%) in the Unna boot group, and in 20 of 28 patients (71%) in the IPC group. Although the difference between groups was not significant, the authors suggested that the combined use of IPC and elastic compression stockings might be preferable to the use of the Unna boot. Recognizing that a 30 mm Hg stocking does not apply enough pressure in patients with C-6 disease, and that Unna boot-type garments are inelastic and more effective than elastic garments, this study probably underestimates the benefit of IPC in patients with VLUs. Furthermore, the adjunctive use of IPC is likely to be more effective when applied over the compression garment (stocking) because compression is additive.

In another study, 235 patients with venous ulcers received either IPC using a compressor with full-leg cuffs plus "classical" therapy (eg, elastic stockings, anticoagulants, anti-infective dressings, antibiotics) or classical therapy alone.[49] Patients with IPC received 1 hour of IPC therapy per day in addition to routine care. Ulcers healed faster in the IPC group (mean, 20 days) than in the classical therapy group (mean, 3 months). IPC shortened the duration of treatment and facilitated return to an active life when compared to routine care with compression stockings, thus providing support for a wider application of IPC. However, such observations might also reflect the inadequate compression delivered by the stockings.

Nikolovska et al[50] conducted the first study comparing two different IPC regimens on ulcer healing, specifically evaluating the speed of inflation and cycle times. They randomized 104 patients with venous ulcers to rapid or slow-compression IPC devices used for 1 hour daily. Both devices applied the same pressure. No other compression treatment was applied during the study period. The primary endpoint of the study was the incidence of complete ulcer healing by 6 months. The rapid-compression pump operated at three cycles/minute, whereas the slow compression pump operated at one cycle every 3 minutes. Healing occurred more often in patients treated with rapid IPC (86% vs 61%; $P = .004$) and occurred sooner ($P = .001$). This was the first study to demonstrate the clinical benefit of rapid intermittent compression (three cycles/minute) compared to slow intermittent compression, supporting the concept that rapid cuff inflation with cycle times consistent with venous filling times produces better clinical results. Rapid inflation produces higher velocities and shear stress on the vein wall and produces higher arterial-venous gradient. High-shear stress stimulates the endothelium to release nitric oxide,[51,52] which in turn inhibits platelet aggregation and platelet and monocyte adhesion. This indicates that the shear stress produced by IPC induces changes in endothelial cell function producing adaptation of blood vessels, resulting in clinical effects that can be measured, including improved arterial perfusion.

DISCUSSION

It is apparent that compression heals venous ulcers and too few patients are treated with proper compression. Arbitrary treatment duration of 12 or 16 weeks may not be long enough to heal large and chronic venous ulcers; however, with continued compression, success can be achieved. Because VLUs are the sequelae of CVD, patients with healed VLUs remain at risk for ulcer recurrence if the underlying pathophysiology of their condition persists. This observation is borne out by the results of the VenUS I trial, in which 13% of ulcers that had initially healed in patients treated with four-component bandages, and 25% of ulcers treated with short-stretch bandages recurred after 12 months.[11] This is likely the result of too little attention to daily sustained compression. Although bandaging provides effective compression, IPC actively stimulates venous return while favorably affecting a number of other physiologic processes.

The effects of IPC observed in patients with venous ulceration alter the underlying pathophysiology, producing an environment compatible with ulcer healing. Effects such as increased venous return, reduced leg edema, increased endogenous fibrinolysis, reduced intravascular coagulation, and improved arterial (skin) perfusion resulting in increased $TcPO_2$ combine to alter the wound environment in favor of healing. Therefore, it should not be surprising that well-designed clinical studies evaluating IPC added to standard wound care and compression therapy show improved rates of ulcer healing. The observations from these studies led to the suggestions from the American College of Chest Physicians that IPC be used to speed healing large VLUs and those recalcitrant to healing for ≥6 months.[53]

Table II summarizes clinical studies demonstrating improvement in ulcer healing when IPC was added to routine care. Although some reports are inconclusive, a review of their methods reveals a disparity in IPC protocols, pressures, and cycle times, making it difficult to compare one treatment regimen with another. Most of these studies were reported before guidelines for reporting the outcome of venous ulcer treatment were published, emphasizing the importance of complete ulcer healing in preference to healing rate or percent healing. Clearly, there is a need for additional, well-designed clinical trials, which evaluates IPC as adjunctive treatment to standard care, which includes sustained compression.

Data suggest that the use of IPC as an adjunct to sustained compression may be the optimal choice for treating patients with VLUs. However, a number of questions remain with regard to its optimal use. For example, it is not

clear whether there are advantages to the particular type of compression. However, it seems clear that rapid inflation is superior to slow inflation and that IPC which cycles at two to three times per minute is superior to long cycle times (one cycle per 2-3 minutes). Application of the device for 3 to 4 hours per day seems superior, although a critical study on application times has not been performed. It seems intuitive that the longer the application time per day, the better the outcome should be.

Although healing of the ulcer is an important endpoint, preventing recurrence, or, ideally, preventing the ulcer from occurring in the first place, should be viewed as optimal treatment. Proper (sustained) compression is important for the healing of ulcers and preventing their recurrence. Although compliance with IPC protocols has not been an endpoint in previous studies, data suggest that patients may prefer IPC to sustained, graduated compression.[54] Ultimately, healing and preventing ulcer recurrence will improve if compliance with compression therapy is enhanced. The adjunctive use of IPC on the prevention of recurrence has not been studied.

In conclusion, an overview of the literature suggests that IPC speeds healing and increases the number of VLUs healed by providing an environment favorable to wound healing. Improved hematologic and hemodynamic effects and reduced edema are likely major contributors. Well-designed clinical studies in which IPC has been used have demonstrated improved healing. Wider application of IPC in patients with VLUs and further investigation in rigorously controlled studies are warranted.

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