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New insights into the physiologic basis for intermittent pneumatic limb compression as a therapeutic strategy for peripheral artery disease

Ryan D. Sheldon, MS,[a] Bruno T. Roseguini, PhD,[b] M. Harold Laughlin, PhD,[c] and Sean C. Newcomer, PhD,[d] *Columbia, Mo; São Paulo, Brazil; and San Marcos, Calif*

The capability for externally applied rhythmic limb compressions to improve the outcomes of patients with peripheral artery disease has been recognized for nearly a century. Modern technology has permitted the development of portable and cost-effective intermittent pneumatic compression (IPC) systems to be made readily available for affordable at-home use. Mounting clinical evidence attests to the effectiveness of this strategy, with improvements in claudication distance rivaling those seen with exercise training or pharmacologic interventions, or both. However, owing to a lack of mechanistic knowledge, whether current application protocols are optimized for clinical outcomes is unknown. Traditional thinking has suggested that IPC transiently elevates blood flow, which is purported to relieve ischemia, improve vascular function, and promote vascular remodeling. Surprisingly, much ambiguity exists regarding the physiologic stimuli and adaptations that are responsible for the clinical effectiveness of IPC treatment. This review presents and critically discusses emerging evidence that sheds new light on the physiologic and molecular responses to IPC therapy. These novel findings highlight the importance of characterizing the phasic changes in the hemodynamic profile during IPC application. Further, these studies indicate that factors other than the elevation in blood flow during this therapy should be taken into account when designing an optimal IPC device. Lastly, we advance the hypothesis that manipulation of IPC stimulation characteristics could potentially magnify the documented clinical benefits associated with this therapy. In conclusion, recent evidence challenges the physiologic basis on which current IPC systems were designed, and further research to elucidate the basic and clinical outcomes of alternate stimulation characteristics is necessary. (J Vasc Surg 2013;58:1688-96.)

Intermittent pneumatic compression (IPC) therapy shows promise as an effective alternative to conventional treatments for relieving many of the symptoms associated with peripheral artery disease (PAD) in the leg. However, the physiologic basis by which this treatment is effective is an active area of investigation. Interestingly, despite recent advances in the field, the stimulation characteristics (ie, pressure, frequency, etc) currently used by IPC systems have remained relatively unchanged for nearly 40 years.

Our group has recently presented a series of studies that challenge the traditional views that have driven IPC system design and application,[1-6] suggesting that other stimulation characteristics may provide superior clinical utility. Here, we present a review of the current state of our knowledge regarding IPC treatment for PAD. We also provide a critical evaluation of the observations and hypotheses that have motivated IPC application strategies with the intent of encouraging investigations that are not constrained by empiric IPC design.

INTERMITTENT PNEUMATIC LEG COMPRESSIONS AS A TREATMENT FOR PAD

PAD affects >8 million adults in the United States[7] and is strongly associated with high mortality risk, deteriorated exercise capacity, and poor quality of life.[7,8] Daily ambulatory activity and functional capacity are particularly impaired,[9,10] resulting in increasingly sedentary lifestyles and the associated complications.[11] Very few treatment options for PAD consistently ameliorate walking-induced pain and improve exercise capacity.[7,12] Supervised exercise training remains the most effective option for claudicant patients, with improvements in maximal walking distances approaching 150% in some trials.[13] However, because most patients experience pain during exercise and require direct supervision from a health care professional, this strategy remains poorly accessible, costly, and adherence is low.[14] Likewise, surgical options are effective in most cases but are applicable to only a fraction of these individuals.[15] Therefore, there is a clear need to promote cost-effective strategies that are easily accessible, less invasive, and do not require direct clinical supervision.

From the Department of Nutrition and Exercise Physiology, University of Missouri, Columbia[a]; the Department of Biophysics, Universidade Federal de São Paulo, São Paulo[b]; the Department of Biomedical Science, University of Missouri, Columbia[c]; and the Department of Kinesiology, California State University–San Marcos, San Marcos.[d]

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Reprint requests: Sean C. Newcomer, PhD, California State University–San Marcos, Department of Kinesiology, 333 S Twin Oaks Valley Rd, San Marcos, CA 92096 (e-mail: snewcomer@csusm.edu).

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CLINICAL TRIALS

Owing to the relatively low cost and ease of use, IPC therapy overcomes major limitations associated with other treatment options for PAD.[16] The remarkable clinical improvements to this therapy have been well described in a number of recent clinical trials,[17-22] as summarized in the Table. In these trials, as little as 3 to 6 months of daily at-home IPC therapy resulted in increases in absolute claudication distance of 80% to 200%.[17-19,21] This is comparable to the increase after supervised exercise training[14] and greater than that after treatment with cilostazol.[23,24] These trials also reported improvements in limb hemodynamics[17,18] and quality of life[18] after treatment. In fact, a 12-month follow-up study in claudicant patients revealed that the benefits of IPC treatment persist long after termination of treatment,[18] which is likely partly due to improved ambulatory ability in these patients.

In addition, IPC is highly effective at treating critical limb ischemia (CLI) with rest pain or tissue loss, or both. A study by Kavros et al[20] assessed the long-term outcomes of IPC in claudicant patients compared with age-matched and disease-matched controls receiving standard care and demonstrated that IPC treatment markedly improved complete limb healing and reduced below-knee amputation at 18 months after treatment. Further, in a cohort of 171 CLI patients, Sultan et al[22] reported a 94% limb salvage rate at a 3.5-year follow-up, and 63% of the patients were free from major adverse clinical events at 4.5 years. These data clearly substantiate the use of IPC therapy in the treatment of claudication and CLI.

The use of IPC to treat complications associated with peripheral arterial insufficiency in other patient groups, such as in diabetic patients or in those with spinal cord injury, is currently not reported in the literature. Many of the clinical trials listed in the Table included diabetic patients, but whether this condition disproportionately affects responsiveness to IPC is unknown or unreported. Spinal cord patients, who not only suffer from PAD but also are at risk for venous stasis and thrombosis due to their immobility, may also benefit from IPC therapy. Similarly unknown is whether IPC is effective when heavy vessel calcification is present or in patients with prior surgical interventions. Future work with IPC will likely reveal a much broader scope for its clinical application than is currently appreciated.

PHYSIOLOGIC MECHANISMS OF IPC ACTION

The clinical evidence provided in the previous section clearly substantiates the benefits of IPC therapy in the treatment of PAD. However, it is unknown whether the stimulation characteristics (ie, pressure, frequency, duration, etc) of commercial IPC devices are optimized for clinical efficacy because no trial has examined dose-response relationships among patients with these characteristics. To this end, it is vital that we seek to understand the mechanism(s) by which IPC is effective. Current thinking in this area implicates increases in hemodynamic shear stress (SS) during IPC application as the primary adaptive mechanism to this therapy by inducing such adaptations as improved endothelial function and collateral artery growth. In this section, we discuss the stimulus provided by IPC and the resulting adaptations.

PATHOPHYSIOLOGIC IMPORTANCE OF HEMODYNAMIC SS

Endothelial cells (ECs) are highly responsive to alterations in hemodynamic SS. Elevated SS is vasoprotective, whereas oscillatory SS (ie, antegrade and retrograde shear within a cardiac cycle) increases oxidative stress, vasoconstrictor production, and causes EC dysfunction. In fact, acute induction of oscillatory SS is sufficient to induce EC dysfunction in healthy arteries in humans.[25] EC dysfunction precedes and is present through all stages of atherosclerotic disease,[26] and atherosclerotic plaques preferentially form in regions of the arterial tree chronically subjected to low net or oscillatory shear profiles, or both, such as is present in bifurcations. Importantly, exercise training improves EC function, partly due to transient elevations of SS during the exercise bout.[27] Similarly, repeated within-session alterations in limb hemodynamics by IPC application may drive adaptations in vascular function that are critical for the clinical effectiveness of this treatment. Indeed, elevated blood flow (although not SS per se) during IPC application has been described in healthy volunteers and in patients across a spectrum of PAD severity.[28-31] Although important questions regarding the hemodynamic stimulus induced by IPC application remain, such as the effects of oscillatory shear during IPC cuff inflation (discussed in detail below), elevated SS is regarded to constitute the adaptive stimulus to IPC treatment.

ADAPTATIONS TO IPC THERAPY

It is widely held that IPC introduces a favorable hemodynamic environment to the treated limb. This hyperemia is speculated to induce two key adaptations within treated limbs of patients with PAD: collateral artery growth and improved EC function. Collateral artery growth is a reported outcome to IPC therapy,[32,33] although this has not been confirmed to date by controlled clinical studies. van Bemmelen et al[32] used bilateral femoral ligation in rabbits as a preclinical model of PAD. After 4 weeks of daily IPC application, the size and density of collateral arteries were greater than in the ligated, untreated control limb. Further, a small cohort of patients with CLI who received IPC treatment experienced angiographic improvement and limb salvage.[33,34] This suggests that vascular remodeling may be a clinically significant adaptation to IPC treatment.

A second key adaptation to IPC therapy is thought to be improved EC function owing to the hyperemic response to treatment application[17,18,21,29-31,35-37] although, surprisingly, no study to date has directly measured endothelial function in response to chronic IPC treatment. However, limited evidence supports this theory. In some clinical trials, for example, the postexercise ankle-brachial

Table. Summary of existing clinical trials examining the effects of intermittent pneumatic compression (*IPC*) treatment on peripheral arterial disease (PAD) outcomes

Ref	*IPC device*	*Study design*	*Subject information*	*Hours/days*
17	FM220[a]	Prospective	Stable claudication (n = 30) Mean age: 59 years Diabetes: EX Smoking: EX Prior revascularization: EX	2
18	AA1000[b]	Prospective (12-month follow-up)	Stable claudication (n = 41) Mean age: 67 years Diabetes: n = 7 Smoking: n = 6 Prior revascularization: NR	>2.5
19	AA1000[b]	Prospective	Stable claudication (n = 34) Mean age: 67 years Diabetes: n = 7 Smoking: n = 11 (current), n = 21 (former) Prior revascularization: EX	3
20	ArterialFlow[c]	Retrospective (18-month follow-up)	CLI (n = 48) Mean age: 70 years Diabetes: n = 32 Smoking: n = 6 (current), n = 34 (former) Prior revascularization: n = 36	6 (three 2-hour sessions)
21	AA1000[b]	Prospective	Stable claudication (n = 30) Mean age: 70 years Diabetes: n = 14 Smoking: n = 10 (current) Prior revascularization: EX	2 (two 1-hour sessions)
22	AA1000[b]	Prospective (1-62-month follow-up, mean 13 months)	CLI (n = 171, no controls) Mean age: 75 years Diabetes: n = 67 Smoking: n = 114 (current + former) Prior revascularization: EX	6-8 (two 3- to 4-hour sessions)

ACD, Absolute claudication distance; *BKA,* below-knee amputation; *CLI,* critical limb ischemia; *EX,* excluded; *ICD,* initial claudication distance; *MACE,* major adverse clinical events; *NR,* not reported; *pe-ABI,* postexercise ankle-brachial index; *r-ABI,* resting ankle-brachial index.
[a]FlowMedic, Caesarea, Israel.
[b]ACI Medical Inc, San Marcos, Calif.
[c]DJO, Vista, Calif.

index was improved but the resting ankle-brachial index was not,[17,18] which may suggest a functional adaptation. In addition, elevated endothelial nitric oxide synthase expression was reported after a single IPC session in rats,[38,39] although a single session of IPC application in healthy human volunteers revealed no acute effect on vascular function.[5] Future studies must address the occurrence and relative importance of changes in vascular function to the clinical outcomes of this treatment.

IPC SYSTEM DESIGN AND RATIONALE

In the previous sections, we have described the clinical improvements ascribed to IPC treatment and summarized current knowledge regarding the physiologic mechanisms driving these changes. In this context, we will now outline the rationale that has driven the design of contemporary IPC systems and then identify three key limitations to the current model.

Historical background. As early as the 1930s, Herrman and Reid[40] were among the first to propose that periodic alternation of the pressure around an extremity could promote hyperemia and relieve atherosclerotic ischemia through a "sucking" effect and be a valuable option to treat PAD. They designed a device that would apply consecutive cycles of negative (−80 mm Hg) and positive pressure (40 mm Hg) around the lower extremity, which resulted in major improvements in 63 of the 75 patients with PAD.[40] Unfortunately these remarkable

Table. Continued.

Treatment duration	*Stimulation characteristics*	*Application site*	*Major outcomes of IPC treatment*
3 months	3-second compressions 3 compressions/min 65 mm Hg	Calf only	85% increase in ICD 75.5% increase in ACD 97% increase in pe-ABI
5 months	4-second compression 3 compressions/min 120 mm Hg	Foot + calf	197% increase in ICD 212% increase in ACD r-ABI increased from 0.59 to 0.69 pe-ABI increased from 0.22 to 0.36 Improved quality of life assessment scores Effects maintained 12-months post treatment
6 months	4-second compression 3 compressions/min 120 mm Hg	Foot + calf	Up to 2.83-fold increase in ICD and ACD Improved r-ABI 28% increase in resting arterial inflow Effects maintained 12-months post treatment
NR	2-second compressions 3 compressions/min 85-95 mm Hg	Calf only	Complete limb healing in 58% vs 17% in controls BKA rate of 42% vs 83% in controls Improved cutaneous oxygenation
12 months	4-second compression	Foot + calf	151% increase in ICD
3 months	4-second compression 3 compressions/min 120 mm Hg	Foot + calf	Resolved rest pain Dry, nonprogressive gangrene Ulcer healing in all but five patients 36.3% increase in toe pressure 57.9% increase in popliteal velocity 30% sustained clinical improvement at 3-year follow-up Limb salvage rate of 94% at 3.5-year follow-up 31% all-cause survival at 4-year follow-up 63% free from MACE at 4.5-year follow-up

results were not immediately recapitulated, because the devices at this stage were large, cumbersome, and not amenable for home-based applications, as indicated in the review by Morris.[41]

Modern IPC system design. IPC systems have since evolved into a cost-effective, highly compact, portable format. However, despite the clear clinical benefit of these systems, the underlying principles driving their design appear to be more dogmatic than scientific. Specifically, stimulation characteristics (ie, pressure, frequency, etc) of modern IPC systems appear to arise from two basic premises: (1) that the hyperemic response to cuff deflation is the primary adaptive mechanism to IPC treatment and (2) that this hyperemic response is a consequence to an augmented arterial-venous (A-V) pressure difference. For the sake of clarity, these premises will hereby be collectively referred to as the A-V hyperemia hypothesis.

These criterion were used to design commercially available IPC devices that deliver two to four rapid (<0.5 seconds to inflate/deflate) compressions per minute at a pressure of 65 to 120 mm Hg in an effort to maximize the A-V pressure difference and, subsequently, the hyperemic response. This pressure is intermediate between typical venous pressure and arterial pressure, allowing for expulsion of venous blood and decreased venous pressure without a meaningful effect on arterial pressure.[42]

The origins for compression frequency stem from the observation by Gaskell and Parrott[43] in 1978 that veins

refill slowly within the first 15 seconds after cuff deflation and that increasing compression frequency would not provide additional benefit. In fact, these authors proposed that a higher compression frequency would actually impair the hyperemic response because cuff inflation impairs conductance of the limb.[43] In contrast, we have recently shown that, at least at the onset of IPC, increased compression frequency does not impede average arterial inflow due to increased blood velocity during cuff deflation compared with low-frequency treatment.[5]

In a seminal report in 2000, Delis et al[44] sought to determine the optimal stimulation characteristics of IPC using venous pressure during application as their outcome variable. That arterial hemodynamics, vascular function, and other responses to IPC were not measured in this effort underscores the widespread acceptance and perceived importance of the A-V hyperemia hypothesis. In their concluding remarks, they suggested that "IPC $_{\text{foot+calf}}$ is the most effective in emptying the leg veins. The optimum stimulus is achieved when an applied pressure level of 120 mm Hg to 140 mm Hg is combined with a frequency of 3 or 4 impulses/min . . .".[44] Higher compression frequencies were not tested.

To their credit, this is the only report in the literature that has attempted to optimize IPC protocols. As such, this recommendation has been used in commercially developed devices such as the Art Assist AA1000 (ACI Medical, San Marcos, Calif), although this application is not universal (Table). However, one must recognize that this conclusion presumes that the A-V hyperemia hypothesis is true. This supposition heeds neither the potential for factors other than the A-V pressure difference to cause hyperemia nor the possibility that other stimuli independent of hyperemia may account for IPC outcomes. In the following sections we will discuss the limitations with this approach to IPC application with the goal of encouraging efforts to optimize stimulation characteristics.

LIMITATIONS TO THE CURRENT MODEL

The A-V pressure gradient does not fully account for the hyperemic response to IPC. A key oversight of the A-V hyperemia hypothesis is that it ignores other factors that affect arterial blood flow, namely, enhanced leg vascular conductance. Indeed, increased hemodynamic shear, such as is reported to occur during IPC application, is well known to induce vasodilation and, likewise, decrease peripheral resistance. Although no study has directly examined the vasodilatory response to IPC, in 1994 van Bemmelen et al[31] suggested that the A-V pressure difference was unlikely to explain the magnitude of the observed hyperemic response to IPC application and proposed a vasodilation mechanism. In 2005, Delis and Knaggs[45] demonstrated that the pulsatility index, an index of peripheral resistance, is maximally attenuated within 5 seconds after the termination of acute IPC application and returns to baseline within 35 to 50 seconds. These findings are consistent with endothelial vasodilatory kinetics and are suggestive that active vasodilation is present during IPC application.

Numerous experimental models support this concept. Increased endothelial nitric oxide synthase expression was reported after a single IPC session in rodents[39] and using an in vitro system designed to study the combined effects of pulsatile forward flow and intermittent compression on cultured ECs.[46] Kirby et al[47] demonstrated mechanically induced vasodilation rapidly occurs within one to two cardiac cycles from the onset of forearm compression in humans. In addition, externally applied pressure pulses induce vasodilation in isolated rodent soleus feed arteries.[48] Finally, arterial inflow is independent of the volume of venous blood expelled by muscle contraction.[49]

Collectively, these data suggest an important role for active vasodilation in the hyperemic response to IPC application. A number of authors have recognized this possibility,[17,18,28,31,35] although the extent to which IPC induces vasodilation has yet to be determined. Acknowledging that rapid vasodilation contributes to the hyperemic response to IPC therapy refutes the traditional notion that IPC should be applied at a low frequency to take advantage of the A-V difference.

The hemodynamic impacts of IPC may be detrimental. Elevated blood flow, although not SS per se, during IPC application has been described in healthy volunteers and in patients across a spectrum of PAD severity.[28-31] The reported magnitude of this hyperemic response is remarkable. IPC application increases mean popliteal artery blood flow by as much as 240%[30] and mean foot skin perfusion by as much as 328% compared with resting values.[28] However, mean blood flow measurements mask important transient changes in limb hemodynamics during IPC. Rhythmic limb compressions result in a low net/highly oscillatory shear profile during the inflated phase with a subsequent high net/low oscillatory shear profile when the cuff is deflated, as shown in Fig 1.[3,5] It is possible that this periodicity in opposing shear stimuli may counterbalance each other, yielding no net effect on vascular function.[5]

Alternatively, repeated transient exposure to this negative stimulus may lead to a protective beneficial adaptation in the vessel by, for instance, increasing antioxidant capacity to counter oscillatory shear-induced oxidative stress. In addition, the hemodynamic response to IPC is not necessarily constant with respect to time,[5] which is important because a single session of IPC treatment can last for durations of 1 to 4 hours or more.[17,18,21,22,50] We have reported in young, healthy volunteers that the hyperemic response to IPC is ablated by the 45th minute of high-frequency IPC application with an increased oscillatory shear profile.[5] This suggests that longer IPC session durations may not provide additional benefit or may even be deleterious. These theories remain speculative, however, because no study to date has directly assessed endothelial function in response to chronic IPC treatment.

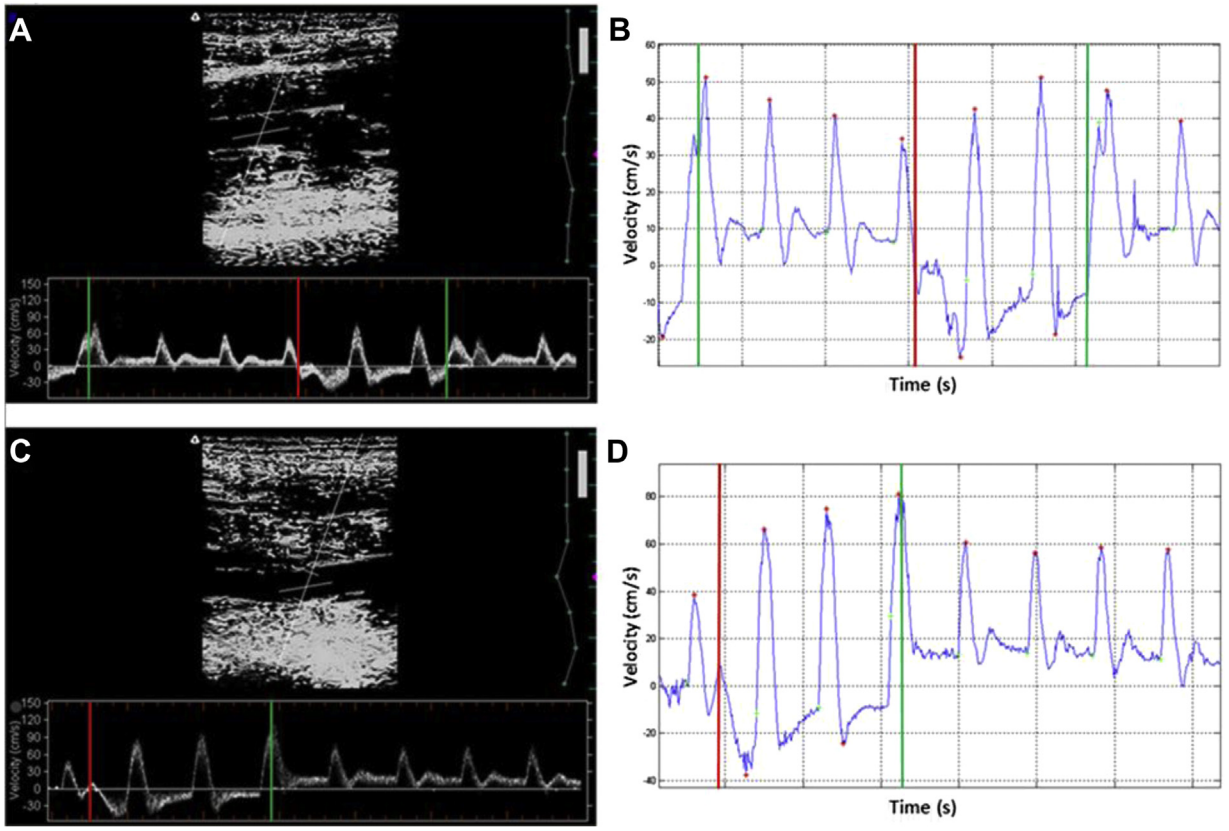

Fig 1. Representative samples of **(A** and **C)** ultrasound/Doppler recordings and **(B** and **D)** corresponding digitalization **(B** and **D)** of limb hemodynamics during **(A** and **B)** high-frequency and **(C** and **D)** low-frequency intermittent pneumatic compression (IPC) treatment. The *red lines* indicate cuff inflation, and the *green lines* indicate cuff deflation. Note the oscillatory shear that occurs during cuff deflation during each respective treatment frequency. Importantly, high-frequency IPC doubles the proportion of each minute the limb is exposed to this state of oscillatory shear but has no acute detrimental effect on popliteal artery function. Figure adapted from Sheldon et al.[5]

Mechanical compression of skeletal muscle is a powerful physiologic stimulus. Another important limitation of current IPC design is that it ignores other stimuli that are elicited by IPC. Mechanical compression of skeletal muscle is one such stimulus. Externally applied pressure is directly transmitted within the tissue, and rises in both intramuscular and transmural pressures are possible mechanisms capable of signaling positive adaptations within the compressed limb.[51] For example, mechanical stimuli can induce structural vascular adaptations in the skeletal muscle. Rivilis et al[52] revealed increased vascular endothelial growth factor (VEGF) expression after shear or muscle stretch, whereas matrix metalloproteinase 2 expression was only elevated after the muscle-stretch stimulus.

Our group recently demonstrated that higher IPC frequency (2 seconds of inflation/2 seconds of deflation in rats, 2 seconds of inflation/3 seconds of deflation in humans), which increases the mechanical stimulus of IPC, in contrast to a common clinical frequency (3 seconds of inflation, 17 seconds of deflation) in the healthy limbs of rats and humans, resulted in a differential expression in skeletal of genes regulating inflammation (monocyte chemoattractant protein-1 [MCP-1], rats) extracellular matrix stability (cysteine-rich angiogenic inducer 61, connective tissue growth factor; humans) and angiogenesis (VEGF, rats).[1,5]

Further, acute IPC application in a rat model of peripheral arterial insufficiency (femoral ligation) revealed a compression frequency-dependent increase in messenger RNA expression of and immunostaining for chemokine (C-X-C motif) ligand 1, MCP-1, and VEGF in skeletal muscle as well as an increase in MCP-1 messenger RNA expression in collateral arteries.[4] These effects occurred despite the seemingly detrimental shear profile that occurs with high-frequency IPC,[5] further supporting an important role for mechanical stimuli and vascular remodeling to the effectiveness of IPC. However, a 2-week application of high-frequency IPC in our rat model of peripheral arterial insufficiency failed to evoke an observable increase in capillary contacts per fiber ratio compared with sham-treated control limbs.[6] This treatment did, however, significantly improve treadmill exercise capacity and in situ skeletal muscle blood flow compared with sham-treated controls.

Longer treatment durations may be necessary to observe morphologic changes in the treated limb. In fact,

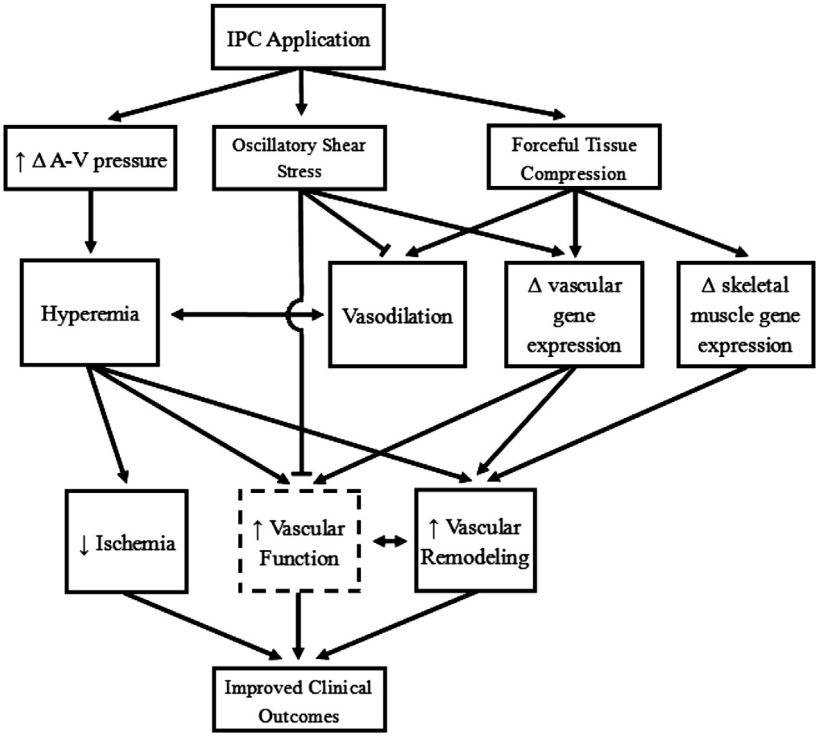

Fig 2. Schematic representation of the proposed mechanisms that contribute to the clinical outcomes (ie, reduced resting and intermittent claudication, improved ankle-brachial index, improved limb salvage, and better quality of life) of intermittent pneumatic compression (*IPC*) therapy. The *dashed-line box* indicates that improved vascular function to IPC treatment is speculative because it has not been directly measured previously, as detailed in the text. *A-V*, Arterial-venous.

cyclic strain and vessel compression can induce vasodilation and improve endothelial function[53-56] and thus provides a possible mechanism through which increasing mechanical strain may also improve blood flow responses and vascular function. It would be of interest for future studies to test this hypothesis by comparing the clinical outcomes of claudicant patients exposed to high-frequency IPC or traditional low-frequency IPC.

Of course, other stimulation characteristics, such as pressure and duration of compression, may also affect IPC efficacy. For instance, although our group has demonstrated no effect of moderate IPC pressure increases in the forearms of humans (150 mm Hg) or the hind limbs of rats (200 mm Hg),[1,3] the use of much higher pressures (~300 mm Hg) and frequencies (one per cardiac cycle) during enhanced external counterpulsation improves brachial and femoral artery function.[57] In addition, ischemic-preconditioning treatment (5 minutes of ischemia at 200 mm Hg, followed by 5 minutes of reperfusion) can improve systemic markers of inflammation.[58,59] Investigation into the utility of such stimulation characteristics in the context of IPC therapy is needed.

In summary, the A-V hyperemia hypothesis is an oversimplified model to describe the mechanisms by which IPC is effective that is supported by limited experimental evidence. It is challenged by recent observations that applying IPC stimulation characteristics that diminish the hemodynamic effect to treatment actually generate a more robust change in vascular and skeletal muscle gene expression without acutely affecting vascular function. Direct mechanical skeletal muscle compression can potentially explain the adaptations that occur to IPC. Importantly, the studies we have referred to used healthy or preclinical models, and whether similar phenomena will occur in the diseased limbs of PAD patients treated with IPC is currently unknown. A schematic of the proposed mechanisms contributing to the outcomes of IPC treatment is depicted in Fig 2. It is crucial that future studies examine these mechanisms in PAD patients.

CONCLUSIONS AND PERSPECTIVES

Owing to its low cost and ease of use, IPC treatment is an attractive alternative to other treatments for PAD. Although IPC has been reported to improve claudication distance to a similar extent as exercise, we must emphasize that this treatment should not be used as an exercise replacement. The substantial systemic benefits of exercise, such as improved oxygen consumption, metabolic regulation, and weight loss, cannot be mimicked by IPC treatment. Ideally, IPC should be used in combination with

exercise in a fashion that progressively increases ambulation time and decreases the time spent with IPC treatment. Future research needs to assess the outcomes of patients using a combined IPC and exercise treatment regimen.

Clinical investigations into the efficacy of IPC provide promising evidence that this treatment is advantageous. However, the IPC systems used in these studies were designed based on premises that overemphasize the importance of the A-V pressure difference and the resulting hyperemic response to treatment. In fact, IPC causes a detrimental oscillatory shear profile during cuff inflation. Importantly, accumulating evidence supports the importance of rhythmic mechanical deformation of skeletal muscle as an important stimulus driving adaptations to IPC therapy. This concept, however, remains to be demonstrated in a clinical setting. Ultimately, various IPC stimulation characteristics and their consequent physiologic responses must be evaluated in the context of the adaptations and clinical outcomes of treatment in chronic, sham-controlled trials.

AUTHOR CONTRIBUTIONS

Conception and design: RS, BR, ML, SN
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Critical revision of the article: RS, BR, ML, SN
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RS and BR contributed equally to this review and share first authorship.

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