Integrity of venoarteriolar reflex determines level of microvascular skin flow enhancement with intermittent pneumatic compression

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Objective: To investigate whether intermittent pneumatic compression (IPC) augments skin blood flow through transient suspension of local vasoregulation, the veno-arteriolar response (VAR), in healthy controls and in patients with peripheral arterial disease (PAD).

Methods: Nineteen healthy limbs and twenty-two limbs with PAD were examined. To assess VAR, skin blood flow (SBF) was measured using laser Doppler fluxmetry in the horizontal and sitting positions and was defined as percentage change with postural alteration [(horizontal SBF − sitting SBF)/horizontal SBF × 100]. On IPC application to the foot, the calf, or both, SBF was measured with laser Doppler fluxmetry, the probe being attached to the pulp of the big toe.

Results: Baseline VAR was higher in the controls 63.8 ± 6.4% than in patients with PAD (31.7 ± 13.4%, *P* = .0162). In both groups SBF was significantly higher with IPC than at rest (*P* < .0001). A higher percentage increase with IPC was demonstrated in the controls (242 ± 85% to 788 ± 318%) than in subjects with PAD, for each one of the three different IPC modes investigated (98 ± 33% to 275 ± 72%) with IPC was demonstrated. The SBF enhancement with IPC correlated with VAR for all three compression modes (r = 0.58, *P* = .002 for calf compression, r = 0.65, *P* < .0001 for foot compression alone, and r = 0.64, *P* = .0002 for combined foot and calf compression).

Conclusion: The integrity of the veno-arteriolar response correlates with the level of skin blood flow augmentation generated with intermittent pneumatic compression, indicating that this may be associated with a transient suspension of the autoregulatory vasoconstriction both in healthy controls and in patients with PAD. (J Vasc Surg 2008;48:1509-13.)

Intermittent pneumatic compression (IPC) devices have been used to improve lower limb perfusion.[1-3] When assessed by laser Doppler flowmetry or duplex ultrasound, substantial increases in cutaneous and arterial blood flow during IPC application have been reported.[1,3-6] Different mechanisms through which IPC induces a circulatory augmentation have been discussed and studied. An undisputed mechanism is the reduction of venous pressure in the dependent foot by IPC, as blood is expelled from the foot and calf to the thigh.[7] This results in a greater arteriovenous pressure gradient and hence augmentation of arterial inflow. A putative mechanism is the transient suspension of local vasoregulation, the veno-arteriolar response (VAR).[8-12] In the sitting position, venous distension occurs, eliciting a precapillary vasoconstriction, and hence a decrease of capillary inflow. When blood is expelled from the veins of the lower extremities, venous pressure de-

creases and the precapillary sphincter dilates. This reduction in resistance may result in elevated arterial inflow. Previous studies have shown that the VAR in patients with peripheral arterial obstructive disease (PAD) is impaired, possibly as an adaptive response to a lower arterial perfusion and pressure.[9,11,13,14] Assuming that IPC produces blood flow increase by temporarily abolishing postural vasoconstriction, the effect of IPC might depend at least in part on the VAR. We hypothesized that the integrity of postural vasoregulation may correlate with blood flow augmentation on IPC application.

MATERIALS AND METHODS

Study groups. The effects of IPC on foot skin blood flux were evaluated in 19 limbs of 15 healthy volunteers (controls) and in 22 limbs of 14 patients with intermittent claudication due to PAD.

Inclusion and exclusion criteria. All studied subjects underwent clinical examination and lower limb arterial and venous investigation that entailed duplex scanning and determination of ankle-brachial pressure indices (ABI) at rest and after exercise challenge on a treadmill. ABI was determined by dividing the higher ankle pressure (obtained from the dorsalis pedis or posterior tibial arteries) by the higher of the two brachial artery pressures after a 15-minute resting period and immediately after treadmill exercise challenge (3.8 km/h, 10% gradient, one minute) for the resting and post-exercise pressure indices, respectively. PAD patients had a long-term history of intermittent claudication (> two years and Rutherford

Table. Baseline characteristics of controls and patients with stable claudication

	Controls	PAD
Age (years)[a]	70 (65-83)	71 (61-84)
Gender ratio (M:F)	10:5	10:4
Risk factors, n (%)		
Smoking	8 (60)	9 (64)
Hypertension[b]	6 (40)	9 (64)
High cholesterol[c]	6 (40)	8 (57)
Ankle: brachial pressure		
index[a]	1.05 (1.02-1.10)	0.71 (0.52-0.85)

[a]Values are mean (range).
[b]Includes subjects on medications with normalized blood measurements at the time of investigation.
[c]Total cholesterol level > 240 mg/dL/ low-density lipoprotein level > 160 mg/dL/ high-density lipoproteine (<40 mg/dL)/ antilipemic medication.

stages I-III), that was confirmed by a reduced ABI at rest or after exercise (<0.9). Duplex ultrasonography documented infrainguinal arterial obstruction invariably pertaining to the superficial femoral. Patients with significant aortoiliac disease on duplex scan (>50% diameter stenosis) were excluded. Peak systolic velocity ratios ≥2.0 were used to account for (in the superficial femoral artery) or exclude (in the aortoiliac arterial segment) 50% or more luminal diameter stenosis.[15,16] Exclusion criteria included chronic venous disease (CEAP ≥ 2), diabetes mellitus, sensory neuropathy (clinically), previous lumbar sympathectomy, critical limb ischemia, gangrene/ ulcerations and use of vasoactive drugs. There were no significant differences between the age- and gender-matched controls and patients with PAD with regard to cardiovascular risk factors (Table).

Examination and scanning protocol. Subjects were asked to withhold caffeine and nicotine for 12 hours prior to skin blood flow assessment. To assess peripheral postural vasoregulation, the veno-arteriolar response (VAR) was measured by determining skin blood flow (SBF) using laser Doppler fluxmetry in the horizontal and sitting positions prior to IPC application. The VAR was calculated as (SBF horizontal − SBF sitting)/SBF horizontal × 100 (percent). Afterward, all subjects were studied in the sitting position on a high examination couch, with their feet resting hanging off the floor. Foot and calf pads (cuffs) of the IPC system were applied gently, and a resting period of more than 20 minutes was allowed for flow stabilization, during which all subjects remained comfortably seated. IPC was then applied and skin flux measurements obtained, starting from the fifth minute of pump action. Subsequently, the IPC was switched off and the subjects were rested for more than 10 minutes, after which new resting skin flux estimations were obtained. The same protocol was followed to evaluate skin flux prior to and during delivery of the last IPC mode examined.

Skin blood flux/flow was obtained using Laserflo BPM 403 (Vasamedics, St. Paul, Minn) featuring a semiconductor gallium-aluminium-arsenide diode emitting a laser beam with a wavelength of 780 nm. The single point

vertical angle laser probe was attached to the pulp of the big toe. The emitted monochromatic coherent light of the laser Doppler illuminates a tissue hemisphere with a radius of 0.1 to 1.4 mm interacting with the moving blood cells, and a proportion of them produce back-scattering and a fractional frequency shift, which is converted to skin blood flux readings. The mean skin blood flux was estimated by analyzing five-minute laser Doppler fluxmetry recordings on a thermosensitive strip obtained at a speed of 20 mm/min, a sensitivity of 10 to 100, and an average time of five seconds. Every effort was made to ensure good, consistent attachment of the probe to the skin with minimal motion artifacts. Tracings thought to result from suboptimal probe attachment were discarded, and measurements were repeated. All investigations were conducted in a noise-free, temperature-controlled environment (21°-23°C) under optimal resting conditions.

Impulse unit. Intermittent pneumatic limb compression was delivered with the Art Assist 1000 unit (ACI Medical, San Marcos, Calif). This is a mechanical pneumatic pump built around a pneumatic impulse generator which consists of an electrically driven air compressor and an air reservoir venting intermittently into two inflatable plastic pads designed to fit the foot and calf. One large-bore elastic tube connects the unit with each one of the pads. Investigation throughout the study was conducted with the pump operating at the following preset parameters: maximum inflation pressure 120 mmHg, minimum deflation pressure 0 mmHg; inflation rise time 0.3 seconds and inflation time four seconds followed by 16 seconds of deflation (0 mmHg), resulting in three compression cycles min-1. Laser Doppler readings were obtained within the 16 seconds of pressure release over a total time period of five minutes of IPC application.

Statistics. Values are shown as mean ± SEM. Analysis was performed using nonparametric statistics on StatView 4.57 (Abacus Concepts, Berkeley, Calif). For intra-group comparison of the effects of different modalities of IPC, the Friedman test was used. For inter-group comparison, the Mann-Whitney U test was applied. The Spearman rank correlation was used to calculate the relation between VAR and skin blood flow augmentation on IPC.

RESULTS

Skin blood flow (SBF) in the horizontal position was similar between controls and PAD (6.8 ± 2.8 to 7.1 ± 1.5 arbitrary units, P = .68), whereas SBF in the sitting position was significantly lower in the controls (2.1 ± 0.8 vs. 5.3 ± 1.6 arbitrary units, P = .01) (Fig 1). This resulted in a greater VAR in the controls (63.8 ± 6.4%) vs the PAD patients (31.7 ± 13.4%) (P = .02) (Fig 2). All three modes of pressure application produced higher levels of SBF compared with the resting values in both groups (P < .0001). The percentage of SBF increase on IPC was lowest with calf compression alone (242 ± 85% in controls and 98 ± 33% in PAD patients) (Fig 3). Higher levels of SBF percentage increase were achieved in the control group with foot compression and combined foot and calf compression (697 ± 205% and 788 ± 318%
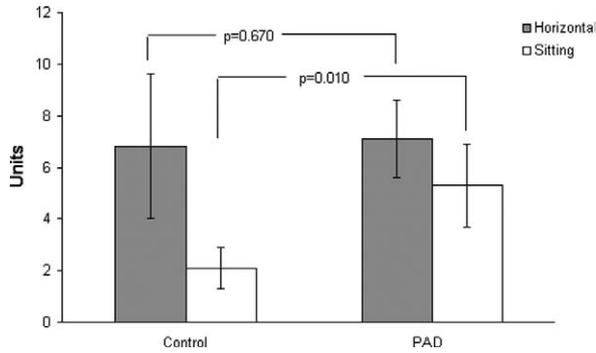
Fig 1. Pedal skin blood flow in recumbent and dependent position in controls and patients with peripheral arterial disease.
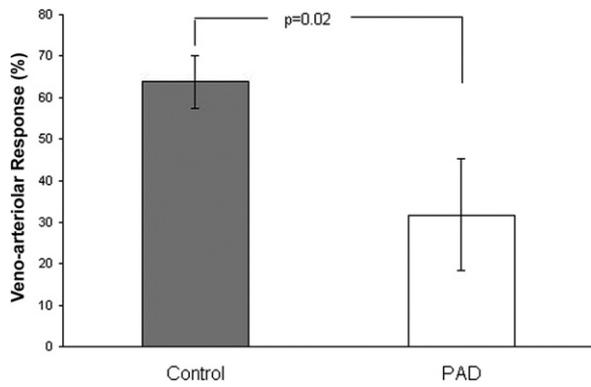

Fig 2. Veno-arteriolar response in controls and patients with peripheral arterial disease.
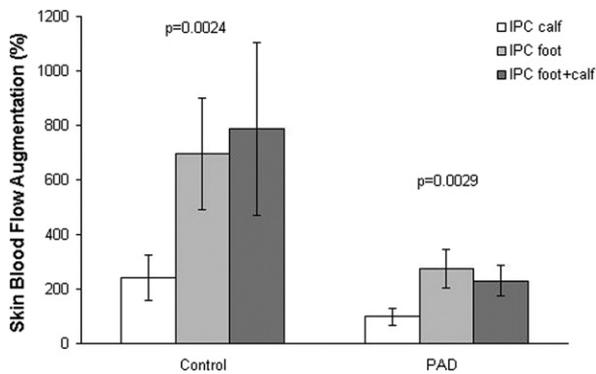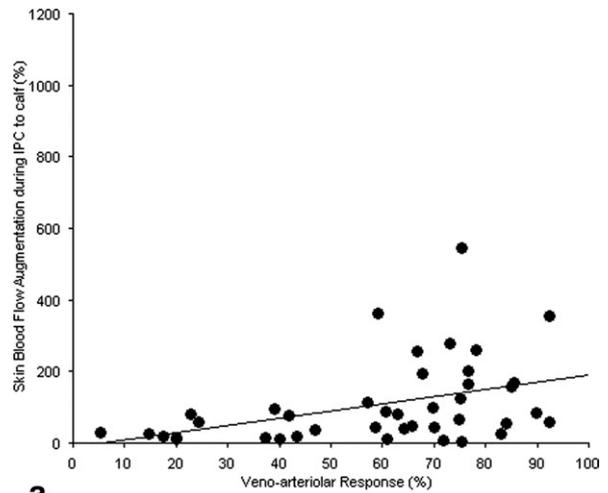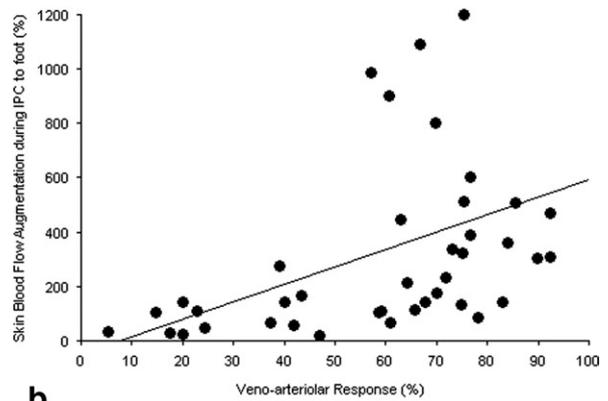

Fig 3. Percentage skin blood flow increase on intermittent pneumatic compression applied to the foot, the calf or both in healthy controls and claudicants.

Fig 4. Spearman correlations between veno-arteriolar response and skin blood flux augmentation (percentage increase) with intermittent pneumatic compression applied to **(a)** the calf (r = 0.58, $P = .002$), **(b)** the foot (r = 0.65, $P < .0001$), or **(c)** foot and calf (r = 0.64, $P = .0002$), both in healthy controls and claudicants.
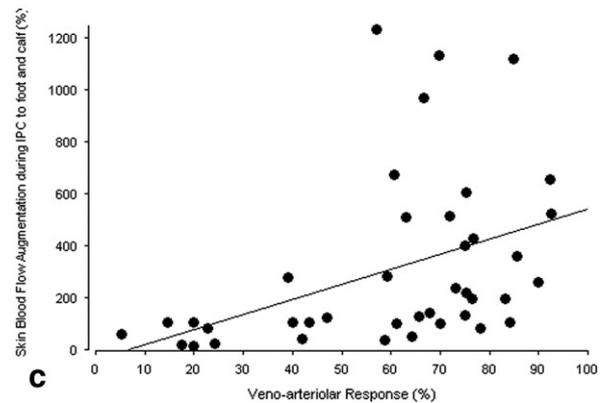
respectively). In PAD patients with foot compression alone or with combined foot and calf compression, the percentage increases were $275 \pm 72\%$ and $230 \pm 57\%$ respectively (Fig 3). SBF with calf, foot, and combined foot and calf compression were significantly higher in the controls compared with PAD patients ($P = .005$, $P = .0158$, and $P = .006$).

There was a significant correlation between the VAR and the SBF augmentation (percentage SBF increase) with all three IPC modes when the controls and the PAD patients were grouped together: r = 0.58, $P = .002$ for calf compression (Fig 4, *a*), r = 0.65, $P < .0001$ for foot

compression (Fig 4, *b*), and r = 0.64, *P* = .0002 for foot and calf compression (Fig 4, *c*). When analysis was performed for the PAD patients only, the VAR correlated well with SBF augmentation on foot (r = 0.69, *P* = .002) and foot and calf (r = 0.65, *P* = .0035) compression, but not on calf compression alone (r = 0.36, *P* = .105). In the control subjects, there was a correlation between the VAR and the augmentation of SBF with IPC, when delivered to the foot (r = 0.55, *P* =.017) and the calf (r = 0.58, *P* = .012), but not when delivered to foot and calf combined (r = 0.45, *P* = 0.15).

DISCUSSION

The study data show that the greater the magnitude of the veno-arteriolar response (VAR) the higher the percentage increase in skin blood flow with IPC, suggesting that a transient attenuation of the VAR during IPC application might be one of the mechanisms through which the latter generates higher levels of blood flow in the lower limb.

Impairment of peripheral sympathetic postural auto-vasoregulation, the local veno-arteriolar response, has been documented in diabetes mellitus, diabetic and alcoholic neuropathy, as well as in PAD.[8,9,13,14] Recent work has shown that the VAR becomes increasingly impaired with PAD progression but is regained after successful bypass grafting or endovascular treatment, suggesting re-adjustment of peripheral resistance.[9,17,18] Improved arterial leg inflow after bypass grafting or endovascular angioplasty is associated with a reversal of peripheral vasodilatation and a decrease in both arterial calf inflow and skin flux on dependency.[17,18] Our data is in accordance with previous studies demonstrating an impaired VAR in patients with intermittent claudication due to PAD.[9,17,19]

In keeping with previous reports, we also found lower levels of skin blood flow augmentation with IPC in patients with PAD than in healthy controls.[1,4,20-22] Different physiologic mechanisms through which IPC induces its flow augmentation effects have been proposed. As previously noted, by expelling the blood from the dependent leg, IPC increases the arterio-venous pressure gradient generating arterial inflow augmentation.[6,7] The increased arterio-venous pressure gradient, however, cannot explain by itself the high level of flow augmentation with IPC observed both in normal limbs and limbs with PAD. A decrease in peripheral resistance has been reported, but the physiologic mechanism involved is not fully understood.[1,3] Increase in the arterio-venous pressure gradient results in release of vasodilatory endothelium-dependent factors in response to shear stress, either by way of increased arterial leg inflow and/or by the transmitted compression impulses.[23,24] Recent work has demonstrated 2- to 2.5-fold up regulation of the endothelial nitric oxide synthase in uncompressed upstream muscle secondary to IPC and its suppression by nitric oxide synthase inhibitor one hour after IPC.[23]

As venous pressure decreases to 25 mmHg or less during most of the deflation time (16 seconds), it could be hypothesized that the veno-arteriolar reflex during the application of IPC is transiently suspended, with subsequent attenuation of

peripheral resistance.[14,25] Our findings suggest that transient suspension of the precapillary vasoconstriction (VAR) is one of the mechanisms by which blood flow would improve with IPC. Additionally, we could demonstrate that a higher skin blood flow on application of IPC is obtained in limbs with more pronounced and hence larger veno-arteriolar responses as shown by a significant correlation between the VAR and skin blood flow augmentation with IPC. In the dependent limb, precapillary vasoconstriction induced by an increase in venous pressure is a physiological mechanism to regulate the hydrostatic arterial pressure augmentation offering protection to the capillary bed. Precapillary vasoconstriction increases peripheral resistance resulting in a lower skin blood flow on dependency. Skin blood flow is lower in healthy limbs than in limbs with PAD in the depending position, as shown in our study and other previous reports.[17,18,26] Therefore, the higher percentage increase in SBF with IPC among healthy limbs mirrors a greater vasodilatory capacity secondary to a stronger vasoconstrictory status in the resting dependent limb. Owing to arterial obstruction at the femoro-popliteal segment and hence the reduced pressure in the distal arteries, the lower VAR is a physiological vascular adaptation in PAD.[9,11]

The present study enhances our insight into these pertinent physiologic mechanisms. Understanding the mechanisms involved in blood flow augmentation with IPC is important for its clinical application. In patients with other disorders that impair VAR (ie, diabetes or chronic venous disorders), the flow enhancing mechanisms of IPC might be different or have a modified effect.[8,27,28] In addition, our understanding of the mechanisms through which IPC enhances blood flow might increase its use, particularly as a recent study has shown an improved limb salvage rate attributable to the use of IPC in patients with critical limb ischemia.[2] With a growing elderly population and an increase in metabolic syndrome, the prevalence of PAD will rise.[29] Different therapeutic modalities are needed to treat patients with limb ischemia. Parallel to surgical and endovascular interventions, there is a need for additional conservative therapeutic measures.[30,31] Further studies need to investigate whether the combination of revascularisation and IPC improves the management of PAD patients. Current knowledge suggests that shear stress and nitric oxide are crucial for angiogenesis.[32-34] In patients with impaired walking distance or even critical limb ischemia, peak shear stress is poor owing to proximal arterial obstruction. Therefore, the application of IPC with a view to enhancing shear stress and arterial leg inflow augmentation might promote angiogenesis.

Limitations of the present study include the small population examined. Also, we evaluated only patients with intermittant claudication, and these data are not directly applicable to patients with critical limb ischemia as the VAR is abolished.[13,14] Because we excluded patients with diabetes mellitus knowing that this disease itself might impair VAR, the relation between VAR and blood flow augmentation by IPC in such patients remains unclear.

In conclusion, skin blood flow augmentation with IPC is associated with a transient suspension of the veno-arteriolar

vasoconstriction of the precapillary sphincter. In support of prior pertinent data, this study reinforces the potential of IPC to emerge as an important mechanical device enhancing skin microcirculation in PAD.

AUTHOR CONTRIBUTIONS

Conception and design: MH, KD
Analysis and interpretation: MH, KD, TW, HHK, SS, EK
Data collection: KD, MH
Writing the article: MH, TW, KD
Critical revision of the article: EK, SS, KD
Final approval of the article: MH, TW, HHK, SS, EK, KD
Statistical analysis: MH, KD
Obtained funding: MH
Overall responsibility: MH, KD

REFERENCES

1. Eze AR, Comerota AJ, Cisek PL, Holland BS, Kerr RP, Veeramasuneni R, Comerota AJ Jr. Intermittent calf and foot compression increases lower extremity blood flow. Am J Surg 1996;172:130-4; discussion 135.
2. Kavros SJ, Delis KT, Turner NS, Voll AE, Liedl DA, Gloviczki P, Rooke TW. Improving limb salvage in critical ischemia with intermittent pneumatic compression: a controlled study with 18-month follow-up. J Vasc Surg 2008;47:543-9.
3. van Bemmelen PS, Mattos MA, Faught WE, Mansour MA, Barkmeier LD, Hodgson KJ, et al. Augmentation of blood flow in limbs with occlusive arterial disease by intermittent calf compression. J Vasc Surg 1994;19:1052-8.
4. Abu-Own A, Cheatle T, Scurr JH, Coleridge Smith PD. Effects of intermittent pneumatic compression of the foot on the microcirculatory function in arterial disease. Eur J Vasc Surg 1993;7:488-92.
5. Labropoulos N, Leon LR Jr, Bhatti A, Melton S, Kang SS, Mansour AM, Borge M. Hemodynamic effects of intermittent pneumatic compression in patients with critical limb ischemia. J Vasc Surg 2005;42:710-6.
6. Delis KT, Knaggs AL. Duration and amplitude decay of acute arterial leg inflow enhancement with intermittent pneumatic leg compression: an insight into the implicated physiologic mechanisms. J Vasc Surg 2005; 42(4):717-25.
7. Labropoulos N, Cunningham J, Kang SS, Mansour MA, Baker WH. Optimising the performance of intermittent pneumatic compression devices. Eur J Vasc Endovasc Surg 2000;19:593-7.
8. Belcaro G, Vasdekis S, Rulo A, Nicolaides AN. Evaluation of skin blood flow and venoarteriolar response in patients with diabetes and peripheral vascular disease by laser Doppler flowmetry. Angiology 1989;40:953-7.
9. Delis KT, GiannouKas AD. Intermittent pneumatic compression (IPC) in the treatment of peripheral arterial occlusive disease (PAOD). A useful tool or just another device? Eur J Vasc Endovasc Surg 2007; 33:309-10.
10. Henriksen O. Local nervous mechanism in regulation of blood flow in human subcutaneous tissue. Acta Physiol Scand 1976;97:385-91.
11. Henriksen O. Orthostatic changes of blood flow in subcutaneous tissue in patients with arterial insufficiency of the legs. Scand J Clin Lab Invest 1974;34:103-9.
12. Henriksen O, Nielsen SL, Paaske WP, Sejrsen P. Autoregulation of blood flow in human cutaneous tissue. Acta Physiol Scand 1973;89:538-43.
13. Wahlberg E, Jorneskog G, Olofsson P, Swedenborg J, Fagrell B. The influence of reactive hyperemia and leg dependency on skin microcirculation in patients with peripheral arterial occlusive disease (PAOD), with and without diabetes. Vasa 1990;19:301-6.
14. Cisek PL, Eze AR, Comerota AJ, Kerr R, Brake B, Kelly P. Microcirculatory compensation to progressive atherosclerotic disease. Ann Vasc Surg 1997;11:49-53.
15. Zierler RE. Duplex and color-flow imaging of the lower extremity arterial circulation. Semin Ultrasound CT MR 1990;11:168-79.
16. Zierler RE, Zierler BK. Duplex sonography of lower extremity arteries. Semin Ultrasound CT MR 1997;18:39-56.
17. Delis KT, Lennox AF, Nicolaides AN, Wolfe JH. Sympathetic autoregulation in peripheral vascular disease. Br J Surg 2001;88:523-8.
18. Husmann MJ, Barton M, Jacomella V, Silvestro A, Amann-Vesti BR. Long-term effects of endovascular angioplasty on orthostatic vasocutaneous autoregulation in patients with peripheral atherosclerosis. J Vasc Surg 2006;44:993-7.
19. Midttun M, Sejrsen P, Paaske WP. Blood flow rate during orthostatic pressure changes in the pulp skin of the first toe. Eur J Vasc Endovasc Surg 1997;13:278-84.
20. Delis KT, Husmann MJ, Cheshire NJ, Nicolaides AN. Effects of intermittent pneumatic compression of the calf and thigh on arterial calf inflow: a study of normals, claudicants, and grafted arteriopaths. Surgery 2001;129:188-95.
21. Delis KT, Husmann MJ, Nicolaides AN, Wolfe JH, Cheshire NJ. Enhancing foot skin blood flux in peripheral vascular disease using intermittent pneumatic compression: controlled study on claudicants and grafted arteriopaths. World J Surg 2002;26:861-6.
22. Delis KT, Husmann MJ, Szendro G, Peters NS, Wolfe JH, Mansfield AO. Haemodynamic effect of intermittent pneumatic compression of the leg after infrainguinal arterial bypass grafting. Br J Surg 2004;91:429-34.
23. Chen LE, Liu K, Qi WN, Joneschild E, Tan X, Seaber AV, et al. Role of nitric oxide in vasodilation in upstream muscle during intermittent pneumatic compression. J Appl Physiol 2002;92:559-66.
24. Dai G, Tsukurov O, Orkin RW, Abbott WM, Kamm RD, Gertler JP. An in vitro cell culture system to study the influence of external pneumatic compression on endothelial function. J Vasc Surg 2000;32:977-87.
25. Eickhoff JH, Engell HC. Local regulation of blood flow and the occurrence of edema after arterial reconstruction of the lower limbs. Ann Surg 1982;195:474-8.
26. Caspary LA, Creutzig A, Alexander K. Orthostatic vasoconstrictor response in patients with occlusive arterial disease assessed by laser Doppler flux and transcutaneous oximetry. Angiology 1996;47:165-73.
27. Jensen K, Andersen K, Smith T, Henriksen O, Melgaard B. Sympathetic vasoconstrictor nerve function in alcoholic neuropathy. Clin Physiol 1984;4:253-62.
28. Belcaro G, Grigg M, Rulo A, Nicolaides A. Blood flow in the perimalleolar skin in relation to posture in patients with venous hypertension. Ann Vasc Surg 1989;3:5-7.
29. Gorter PM, Olijhoek JK, van der Graaf Y, Algra A, Rabelink TJ, Visseren FL. Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Atherosclerosis 2004;173:363-9.
30. Mannava K, Money SR. Current management of peripheral arterial occlusive disease: a review of pharmacologic agents and other interventions. Am J Cardiovasc Drugs 2007;7:59-66.
31. Delis KT, Nicolaides AN. Effect of intermittent pneumatic compression of foot and calf on walking distance, hemodynamics, and quality of life in patients with arterial claudication. A prospective randomized controlled study with 1-year follow-up. Ann Surg 2005; 241(3):431-41.
32. Mendoza MG, Robles HV, Romo E, Rios A, Escalante B. Nitric oxide-dependent neovascularization role in the lower extremity disease. Curr Pharm Des 2007;13:3591-6.
33. Lee HJ, Koh GY. Shear stress activates Tie2 receptor tyrosine kinase in human endothelial cells. Biochem Biophys Res Commun 2003;304:399-404.
34. Li S. Analysis of endothelial cell migration under flow. Methods Mol Biol 2005;294:107-21.