The Role of Low Resistance Blood Flow Pathways in the Pathogenesis and Healing of Venous Leg Ulcers

KEN MALANIN[1,2], PERTTI J. KOLARI[3] and VÄINÖ K. HAVU[1]

[1]Department of Dermatology, University of Turku, Turku, [2]Medical Center of Lappeenranta and [3]Department of Clinical Physiology, South Karelian Central Hospital, Lappeenranta, Finland

In an attempt to clarify the pathophysiology of haemo-dynamics in legs with venous ulcer we investigated the effect of a single intermittent pneumatic compression treatment on the peripheral resistance of leg arteries and the cutaneous laser Doppler flux in the leg. Eight patients with venous leg ulcers and 10 subjects with healthy legs were investigated. Doppler waveforms of the leg arteries and laser Doppler flux of the leg skin were recorded before and after a single inter-mittent pneumatic compression treatment with the subjects in a recumbent position. In the legs with venous ulcer, the peri-pheral resistance of the arteries was lower and the laser Doppler flux was greater, compared with healthy legs ($p = 0.003$ and $p = 0.002$, respectively). A single intermittent pneumatic compression treatment raised the peripheral resis-tance in the arteries of legs with ulcer and laser Doppler flux of the skin more in ulcer legs than in healthy legs ($p = 0.046$ and $p = 0.034$, respectively). These findings suggest that removal of oedema causes redistribution of skin blood flow in the legs with venous ulcer favouring the superficial capillary perfusion. This could explain why compression treatment promotes the healing of venous leg ulcers. *Key words: chronic venous insufficiency; laser Doppler fluxmetry; Doppler ultrasound; arteriovenous shunting; intermittent pneumatic compression.*

In legs with chronic venous insufficiency (CVI), intermittent pneumatic compression (IPC) treatment eliminates oedema, raises transcutaneous skin oxygen tension, enhances the laser Doppler flux, elevates the temperature of the skin and promotes healing of venous ulcers (1–3), while it has no effect on transcutaneous oxygen tension in healthy legs (4). In legs with CVI the cutaneous blood flow is increased (2, 5–10) and the capillaries of the skin are dilated and coiled (11–13). The density of capillaries in the skin has been shown to be dimi-nished in *in vivo* studies (11, 13) and in histological samples (12). Transcutaneous oxygen tension ($TcPO_2$) in legs with CVI has found to be diminished in the majority of investi-gations (5–7, 13, 14) and the oxygen extraction in the lipo-dermatosclerotic skin has been found to be reduced (15).

Premature venous filling in legs with CVI is a common find-ing at angiography (16–18) and the oxygen content in venous blood in such legs has been found to be elevated (16, 19). It has been suggested that these findings are caused by arteriovenous shunting through low-resistance blood flow pathways in the capillary bed (16–18).

On the basis of labelled protein perfusion studies the exis-tence of arteriovenous shunting has, however, been challenged (20–21). In previous studies using duplex scanning, we found that the peripheral resistance is lowered in the arteries of legs with venous ulcer and that there was premature venous filling seen on angiography (22). We subsequently showed that there is a highly significant inverse correlation between the severity of chronic venous insufficiency and peripheral resistance in the leg arteries (23).

There is still a great deal of controversy about cutaneous microcirculation in legs with CVI, and the pathogenesis of venous leg ulceration is not fully understood (24), thus further studies are needed to clarify these issues.

In this study we investigated the effect of a single IPC treat-ment on the peripheral resistance of leg arteries and on laser Doppler flux of the skin in legs with venous ulcer. Our aim was to determine the mechanisms contributing to ulcer forma-tion and to healing of venous leg ulcers.

PATIENTS AND METHODS

The study plan was approved by the Joint Commission on Ethics of Turku University and Turku University Central Hospital.

Patients

After obtaining written consent, 8 patients with venous leg ulcers were investigated (4 women, 4 men). The median age of the patients was 62 years (range 47–76 years). Ten healthy legs of 10 control subjects (6 women, 4 men) were investigated in an identical way. The median age of the control subjects was 62 years (range 47–76 years). The patients and control subjects had no diabetes, peripheral neuropathy or peri-pheral arterial disease. The ankle/brachial systolic blood pressure index (ABI) measured from dorsal pedal and posterior tibial arteries was normal, i.e. 1 or more (25), in all legs with ulcer and control legs. In the legs with ulcer a swelling tendency had existed for 6–35 years (median 20 years) and the duration of ulcers was from 1 month to 5 years 6 months (median 9 months). In 2 legs with ulcers the aetiology of CVI was previous deep venous thrombosis, whereas in others the aetiology was a primary valve damage. Seven patients had had at least 1 venous ulcer period (range 1–5 ulcer periods) previously in the same leg. The simplified CEAP classification of the legs with ulcers is presented in Table I (26).

Investigations

Doppler waveforms were registered from posterior tibial and dorsal pedal arteries using a Multi Dopplex MDII continuous wave Doppler device equipped with a NTD 5 MHz probe (Huntleigh Technology plc, Cardiff, UK). The resistance indices were calculated from the waveforms of Doppler spectra using Reporter software (Huntleigh Technology).

The formulae for resistance indices (RI) are shown in Fig. 1. The RI is more than 1 when there is a reverse flow component in early diastole and the RI is 1 when there is no reverse flow. When there is antegrade flow during the whole diastole the RI is less than 1. The mean of resistance indices of the posterior tibial artery and the dorsal pedal artery was considered to best represent the average peripheral

Table I. *Clinical and anatomical classification of the legs*

	Clinical classification	
Anatomical classification	Class 0	Class 6
P		3
SP		3
SDP		2
Number of legs investigated	10	8

Clinical classification: class 0 = no visible or palpable signs of venous disease; class 6 = leg oedema, lipodermatosclerosis and active ulceration.

Anatomical classification: S = superficial venous insufficiency; D = deep venous insufficiency; P = perforating vein insufficiency. One or more system(s) involved.

arterial resistance in the leg and these mean values are used in the analysis.

Laser Doppler flux was measured with a Periflux 4001 device (wavelength 780 nm) using a standard probe model PF408 (Perimed, Järfälla, Sweden). Zero setting and calibration were performed using a PF1000 calibration device and Periflux Motility Standard fluid (Perimed). The laser Doppler flux values were recorded as arbitrary perfusion units and 250 PU was recorded in the Motility Standard fluid. The offset value was adjusted to 0 PU and time constant to 3.0 s. The data were registered and analysed on a computer using Perisoft software (Perimed). The laser Doppler flux is a factor of the concentration of moving blood cells and the blood cell velocity (27). The components could be differentiated with the Perisoft program. The concentration of moving blood cells and the blood cell velocity are expressed as concentration units (CU) and velocity units (VU), respectively.

To determine the repeatability, sensitivity and operating range of the laser Doppler equipment, a validation experiment (28) was performed on skin on the flexor side of the forearm of 5 healthy adults, with the following results: median (range): resting laser Doppler flux 6.92 (5.66–12.87) PU, laser Doppler flux of biological zero (during arterial occlusion): 2.93 (2.67–4.17) PU, peak laser Doppler flux (after occlusion, during reactive hyperaemia): 47.30 (34.50–61.80) PU and resting laser Doppler flux (after reactive hyperaemia): 6.92 (5.42–13.26) PU.

All the values of the laser Doppler flux, the concentration of moving blood cells and the blood cell velocity are given without subtracting the values for biological zero. Biological zero was recorded only for the validation experiment.

The probe was attached to the skin with a standard probe holder PF 104, using a ring of double-sided adhesive tape. In the legs with ulcers the probe was attached to clinically uninflamed skin 2–6 cm from the border of the ulcer and, in control legs, on the medial part of the leg, 15 cm proximal from the sole of the foot.

A single IPC treatment was given identically to the legs with ulcers and control legs with the subjects in a recumbent position, using the
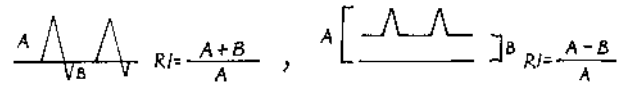

Fig. 1. Formulae for resistance indices (RI). A = Systolic blood flow, B = Diastolic blood flow.

Ventipress IPC device Model 14/4 equipped with a knee-length multi-chamber compression boot (Ventipress Ltd, Lappeenranta, Finland) (29). The end-pressure of compression was 60 mmHg. The inflation time was set at 15 s and the deflation/ventilation time at 30 s. The IPC treatment session lasted for 45 min. During IPC treatment the leg was on a pillow with the heel 20 cm above the bed and 5 cm higher than the knee which was flexed about 25 degrees.

The patients were investigated in a quiet room with an ambient temperature of 22.5 ± 0.5°C. The narrowest circumference of the ankle was measured and another measurement was taken similarly 20 cm proximal from this level, then the volume of leg was calculated using a formula presented by Stranden (30).

Study protocol

The patients were asked not to wear elastic stockings or compression bandages on the legs with ulcers for 3 days before the investigation.

The patient took up a recumbent position then the leg volume was recorded. After a rest of 20–30 min in the recumbent position the laser Doppler flux and the RI were recorded, in that order. After IPC treatment, the subjects were allowed to remain resting in a recumbent position and the recordings were repeated in the same way as before the IPC treatment. All pre- and post-treatment measurements of laser Doppler flux were made at the same sites.

Statistics

The results are expressed as medians and ranges. Statistical tests were performed using the non-parametric Wilcoxon signed rank test for paired comparisons and the Mann-Whitney U test for comparison of the groups. Two-tailed p-values of less than 0.05 were considered significant.

RESULTS

A single IPC treatment reduced the leg volume more in legs with ulcers, i.e. 46 (10–74) ml, than in healthy legs, i.e. 19 (0–29) ml (p = 0.016).

The RI was significantly lower in legs with ulcers than in healthy legs before IPC (p = 0.003). The IPC treatment improved RI in legs with ulcers (p = 0.016), whereas it had no significant effect on the RI in healthy legs (p = 0.391). The improvement in RI in the legs with ulcers was greater than in healthy legs (p = 0.046) (Table II).

Fig. 2 presents an example of RI recordings from the posterior tibial artery and the dorsal pedal artery in 1 leg with ulcer before and after IPC treatment, demonstrating that IPC treatment normalized the lowered RI value.

Before the IPC treatment the RI was fluctuating in the

Table II. *The mean resistance indices (RI) calculated from Doppler waveforms of posterior tibial (PTA) and dorsal pedal (DPA) arteries before and after a single intermittent pneumatic compression (IPC) treatment in 8 legs with ulcers and 10 healthy legs recorded in a recumbent position, median (range)*

	Before IPC treatment	After IPC treatment	Difference	p value
Legs with ulcers	n = 8	n = 8	n = 8	
Mean RI of PTA and DPA	(a) 0.94 (0.77–1.42)	1.11 (0.86–1.47)	(b) −0.12 (−0.43 – −0.01)	0.016
Healthy legs	n = 10	(x) n = 9	(x) n = 9	
Mean RI of PTA and DPA	1.39 (1.18–1.48)	1.39 (1.30–1.48)	−0.01 (−0.22–0.07)	0.391

Ulcer legs compared with healthy legs: (a) p = 0.003; (b) p = 0.046; (x) RI of DPA not obtainable in 1 healthy leg after IPC treatment.
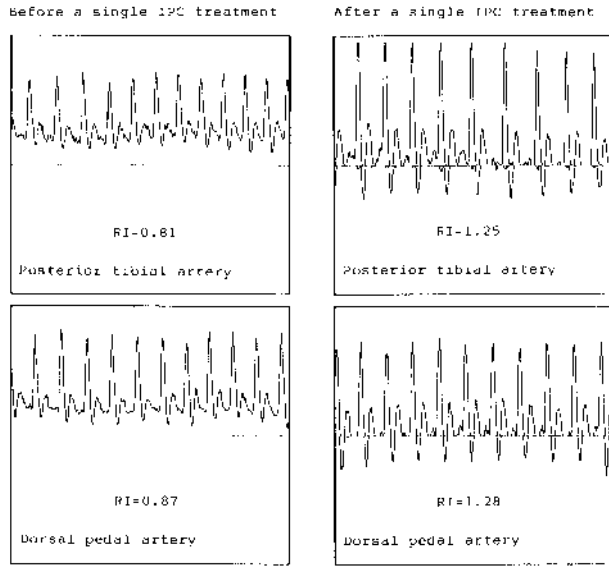
Fig. 2. Doppler waveforms of the posterior tibial and dorsal pedal arteries before and after a single intermittent pneumatic compression (IPC) treatment in 1 leg with ulcers. The peripheral resistance indexes (RI) were low before IPC (RI = 0.81 and 0.87, respectively). After IPC the RI reflects enhanced peripheral resistance (RI = 1.25 and 1.28, respectively).
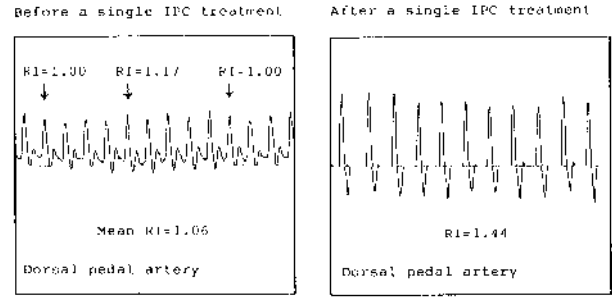

Fig. 3. An example of the observed fluctuation in peripheral resistance of the dorsal pedal artery in 1 healthy leg. The resistance index (RI) ranged from 1.00 to 1.17 (arrows) (mean RI = 1.06). After a single intermittent pneumatic compression (IPC) treatment the fluctuation in peripheral resistance disappeared and the RI was 1.44.

posterior tibial artery in 2 ulcer legs and in dorsal pedal artery in 2 healthy legs. After IPC treatment the fluctuation was no longer detectable. This phenomenon in 1 healthy leg is presented in Fig. 3.

Because the findings of fluctuation of RI, 1 leg of each of 10 additional healthy subjects (6 women, 4 men) were investigated. These subjects' median age was 49 years (range 22–66 years). The RI was recorded from the posterior tibial artery and the dorsal pedal artery immediately after a recumbent position was obtained and every 5 min up to 50 min. The RI values stabilized during 30 min of rest in all other legs except in 2 in which fluctuation of RI in the dorsal pedal artery was present up to the last recording. The fluctuation of RI in these legs varied from 0.94 to 1.28 and from 0.78 to 1.35. The fluctuation of RI of various degrees happened about 4 times in 1 min.

The laser Doppler flux and the concentration of moving blood cell values before the IPC treatment were higher for the legs with ulcers compared with the healthy legs ($p = 0.002$ and $p = 0.0003$, respectively), whereas there was no significant dif-

ference in the blood cell velocity values ($p = 0.829$). The IPC treatment enhanced the laser Doppler flux more in legs with ulcers than in healthy legs ($p = 0.034$). The enhancement of the laser Doppler flux was caused by the increased concentration of moving blood cells which was greater in legs with ulcers than in healthy legs ($p = 0.055$) (Table III).

DISCUSSION

Our results show that in legs with venous ulcers the RI of arteries is reduced and the laser Doppler flux of skin is enhanced compared with healthy legs. A single IPC treatment removed oedema, normalized peripheral resistance in the posterior tibial artery and the dorsal pedal artery and enhanced laser Doppler flux in legs with venous ulcer.

Kolari (31) has found that transmittance of laser light at 820 nm (percentage of emitted light) at various depths of skin is: 63% at 0.4 mm, 37% at 0.9 mm, 13.5% at 1.9 mm, 5% at 2.9 mm and 1% at 4.5 mm. It can thus be estimated that the penetration of the laser light we used (780 nm), is sufficient to register the blood flux in the nutritive capillaries as well as in the deeper vascular network in the dermis. The laser Doppler flux recording reflects the total blood flux in the measurement area and, because the penetration of laser light diminishes in relation to the depth of the skin, the most superficial flux is best represented in the recording. In validating the equipment used, the measured median biological zero was 42% of the median resting laser Doppler flux on skin on the flexor side of the forearm of 5 subjects. The biological zero values on the legs were

Table III. *Laser Doppler flux (LDF) and its components: concentration of moving blood cells (CMBC) and blood cell velocity (BCV) recorded before and after a single intermittent pneumatic compression (IPC) treatment in 8 ulcer legs and in 10 healthy legs recorded in a recumbent position, median (range). PU = perfusion units; CU = concentration units; VU = velocity units*

	Before IPC treatment	After IPC treatment	Difference	p value
Legs with ulcers (n = 8)				
LDF (PU)	(a) 17.27 (9.17–144.46)	33.74 (13.30–204.47)	(d) −9.35 (−108.12–73.05)	0.250
CMBC (CU)	(b) 24.74 (10.52–141.71)	55.48 (19.44–217.15)	(e) −14.73 (−91.55–37.37)	0.109
BCV (VU)	(c) 92.15 (51.20–128.99)	68.17 (42.80–110.24)	(f) 10.79 (−25.87–73.84)	0.148
Healthy legs (n = 10)				
LDF (PU)	8.17 (3.94–15.55)	7.62 (5.13–13.24)	1.13 (−2.66–2.68)	0.322
CMBC (CU)	8.59 (5.32–18.94)	10.10 (4.71–15.02)	−1.28 (−8.69–4.06)	0.160
BCV (VU)	101.09 (65.10–180.69)	77.79 (46.82–136.04)	28.39 (−35.21–68.22)	0.084

Legs with ulcers compared with healthy legs: (a) $p = 0.002$; (b) $p = 0.0003$; (c) $p = 0.829$; (d) $p = 0.034$; (e) $p = 0.055$; (f) $p = 0.829$.

not measured because we wanted to determine the effect of a single IPC treatment on the total laser Doppler flux values of the skin in legs. Thus, the laser Doppler flux values obtained from the legs are presented as such, i.e. in a similar way to that in previous studies (2, 5–10), without subtracting the biological zero (28).

To make it possible to interpret the changes in the laser Doppler flux values, another technique was needed to monitor simultaneously the peripheral circulation in the leg. The Doppler waveforms were therefore registered from the posterior tibial and dorsal pedal arteries and the resistance indices were calculated from the waveforms obtained.

If the circumference of the lower leg is assumed to be a circle, it can be calculated that a single IPC treatment diminished the radius of the lower leg by 0.6 mm (median) (range 0.3–1.1 mm). The IPC treatment compresses all the soft tissues of the leg. Therefore the reduction in the distance between the laser Doppler probe and the capillary bed is less than the reduction in the radius of the leg. Using high frequency ultrasound imaging the oedema has been found to be located in the upper dermis in legs with CVI (32), which is in concordance with the capillaroscopic observations made by Fagrell (11). When this oedema diminishes, the whole capillary bed becomes closer to the laser Doppler probe. This may contribute to the higher flux values observed after a single IPC treatment, but it does not explain the observed elevated (normalized) peripheral resistance in leg arteries after removal of oedema. This strongly suggests that redistribution of blood flow has also occurred. The reduced oedema in the papillary dermis may improve cellular nutrition in the skin by reducing the distance between the nutritive capillaries and the cells of the skin and by reducing the pressure on the capillaries, thus improving blood flow (32).

Belcaro & Nicolaides investigated the effect of a single IPC treatment in 34 limbs with CVI and in 20 limbs of healthy subjects (33). They found that before a single IPC treatment the laser Doppler flux was increased and the venoarteriolar response was diminished in legs with CVI compared with healthy legs. They found that a single IPC treatment diminished the laser Doppler flux and enhanced the venoarteriolar response of the skin in legs with CVI. Other investigators (8, 10, 14), have, however, found the venoarteriolar response to be unaffected in legs with CVI compared with healthy legs. Pryce & Friedmann (9) found the venoarteriolar response to be increased in legs with CVI compared with healthy legs. A single IPC treatment has been found to enhance the laser Doppler flux in legs with CVI (2, 10); this is confirmed by the present study. Because of the contradictory findings in the literature concerning the venoarteriolar response in legs with CVI, there is no strong reason to suggest that the lowered resistance in peripheral arteries in legs with CVI would be caused by the impairment of the venoarteriolar response or that a single IPC treatment could normalize the peripheral resistance in the arteries of legs with CVI by improving the venoarteriolar response.

Many earlier findings suggest the existence of arteriovenous shunting through preferential or low-resistance pathways in the capillary bed in legs with CVI. Despite the dilatation and coiling of the capillaries, the capillary density has been found to be diminished in legs with CVI (11–13), while the cutaneous blood flow is enhanced (2, 5–10). The arterial resistance is lowered at angiography (16–18) and the oxygen content of venous blood is elevated in legs with CVI (16, 19). Accordingly, the transcutaneous oxygen tension ($TcPO_2$) is lowered (5–7, 13, 14) and oxygen extraction is reduced (15) in the skin of legs with CVI. All these findings can reflect enhanced whole skin blood flow while there is ischaemia in the nutritional capillary bed (34).

The elevated basal laser Doppler flux in legs with severe CVI in this study can be explained by accumulation of blood cells in capillaries due to venous stasis (increase in the concentration of moving blood cells). The enhancing effect of IPC on the laser Doppler flux (on its concentration of moving blood cells component) can reflect improved capillary circulation which, together with elevated RI, could be explained by a reduction in arteriovenous shunting. The earlier findings, which showed that IPC raises the transcutaneous skin oxygen tension, elevates skin temperature in legs with CVI (1, 2) and promotes the healing of venous ulcers (3), support this theory.

On the basis of the findings of earlier isotope studies, the existence of arteriovenous shunting has been challenged (20–21). These studies have, however, been done without correlation with angiography. Partsch (35) has suggested that albumin acts like fibrinogen and deposes pericapillarly in the post-thrombotic legs. This may explain why labelled albumin can accumulate near the ulcer (20). Thus, the findings in radio-isotope studies may be misleading in attempts to examine arteriovenous shunting in legs with CVI. In addition, we found in the present study, that the peripheral resistance can fluctuate. This was evident in the posterior tibial artery in 2 legs with ulcers and in the dorsal pedal artery in 4 healthy legs. This phenomenon can also contribute to the findings in radio-isotope studies.

Post-traumatic arteriovenous fistulas can cause leg ulcers (36) and artificial shunts made on the arm for haemodialysis can cause digital ulcers with hyperpigmentation, induration of the skin and pericapillary fibrin formation, all of which are typical features of venous ulcer (37). There is also evidence that diabetic microangiopathy can cause arteriovenous shunting, which may contribute to diabetic foot ulcers (38).

Earlier findings from angiography of the legs with CVI have shown that the arteriovenous shunting can appear both "microscopic", i.e. diffuse (16–18, 22), and/or "macroscopic", i.e. due to local arteriovenous anastomoses (22, 39).

The present study gives no clue as to whether the arteriovenous shunting happens only at the level of the skin of the leg, in the acral parts of the lower extremity, in the muscular circulation, or in all of these.

In conclusion, our results support the hypothesis that arteriovenous shunting through low-resistance blood flow pathways plays a role in the pathogenesis of venous leg ulcers. The present findings suggest that arteriovenous shunting is a dynamic phenomenon dependent on the degree of venous stasis in the leg and that it can be affected by removing leg oedema even with a single intermittent pneumatic compression treatment. The beneficial effect of oedema removal can be explained by the redistribution of blood flow in the skin of legs with venous ulcers, leading to better capillary perfusion and skin nutrition.

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