Eur J Vasc Endovasc Surg **17**, 419–423 (1999)
Article No. ejvs.1998.0801

Oedema in the Lower Limb of Patients with Chronic Critical Limb Ischaemia (CLI)

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Objective: *approximately 70% of patients with chronic critical limb ischaemia (CLI) show clinical signs of oedema in the distal leg and foot. The primary aim of the present investigation was to quantify this oedema. In addition we investigated whether oedema formation could be due to deep venous thrombosis (DVT).*
Methods: *fifteen patients with unilateral CLI and oedema were studied, four males and 11 females, with a mean age of 77 ± 10.3 years. Water displacement volumetry (WDV) was used to measure limb volume. Colour duplex ultrasound (CDU) and venous occlusion plethysmography (VOP) were applied to exclude functionally significant DVT. Blood chemistry was analysed to screen for some causative factors of generalised oedema formation.*
Results: *the mean volume of the limbs with CLI was 9% greater than the contralateral limbs (1279 ± 325 ml vs. 1179 ± 298 ml). None of the patients had functionally significant DVT. The mean plasma albumin concentration was reduced at 28.5 ± 6.6 g/l.*
Conclusion: *a significantly reduced plasma albumin concentration cannot be regarded as a causative factor, since the oedema is unilateral. The aetiology of oedema formation is probably multifactorial, and further investigations are under progress to elucidate relevant pathogenetic factors.*

Key Words: Critical limb ischaemia; Oedema; Water displacement volumetry; Deep venous thrombosis; Colour duplex ultrasound; Plethysmography.

Introduction

According to a recent survey at our department, 43 of 60 consecutive patients with chronic critical limb ischaemia (CLI)[1] had leg and foot oedema in the afflicted limb. Accumulation of fluid in the extracellular space increases the diffusion distance between capillaries and tissue cells, and probably disturbs the exchange of respiratory gases and metabolites.[2] This could lead to a further increase in tissue hypoxia in an already severely ischaemic limb. Knowledge about the pathogenesis of this oedema may have consequences for therapeutical measures, but underlying causative mechanisms have not yet been clearly described.

The magnitude of oedema presumably determines the degree of its deleterious pathophysiological consequences. Thus, the primary aim of this study was to *quantify* the oedema in the lower limb of patients with CLI. A second objective was to investigate whether functionally significant DVT could be a causative factor. Furthermore, the patients were screened for some clinical and biochemical factors that may be associated with generalised oedema formation.

Patients

CLI was defined according to the Second European Consensus Document on CLI:[1] Persistently recurring ischaemic rest pain requiring opiate analgesia for more than two weeks or ulceration or gangrene of the foot or with an ankle systolic pressure ≤50 mmHg or toe systolic pressure ≤30 mmHg. During a period of eighteen months, from September 1996 to March 1998, 15 patients with unilateral CLI and pitting oedema were included (four males and 11 females, with a mean age of 77 ± 10.3 years). All patients suffered from rest pain, six (40%) had gangrene and four (27%) skin ulceration. Patients with signs of local infection were excluded. Seven patients (47%) had heart disease and eight (53%) were being treated for hypertension, two (13%) had a prior stroke and two (13%) diabetes mellitus. Four (26%) suffered from chronic obstructive

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1078–5884/99/050419 + 05 $12.00/0

Table 1. Summary of patient characteristics.

Variable	Yes	No
Rest pain	15 (100%)	0
Ischaemic skin ulcer	4 (27%)	11 (73%)
Gangrene	6 (40%)	9 (60%)
Signs of infection	0	15 (100%)
Heart disease	7 (47%)	8 (53%)
Hypertension	8 (53%)	7 (47%)
Stroke	2 (13%)	13 (87%)
Pulmonary disease	4 (27%)	11 (73%)
Diabetes	2 (13%)	13 (87%)
Smoking	14 (93%)	1 (7%)

lung diseases (COLD), none had renal disease (Table 1). Nine (60%) patients were on antiplatelet therapy, whereas five (33%) used warfarin. Fourteen (93%) patients used tobacco.

Patients with an amputated contralateral limb, bilateral CLI and oedema, clinical signs of congestive heart failure, manifest venous insufficiency or lymphoedema were excluded from the study. The study was accepted by the Regional Ethical Committee of Southern Norway. All patients gave a written consent.

Methods

Ankle and brachial pressures were measured with the ultrasound Doppler technique.[3] In the limbs with CLI where Doppler signals were not detectable, ankle pressure was defined at 15 mmHg.

Water displacement volumetry (WDV)

The patients were investigated in the sitting position. Each limb was carefully placed into a container equipped with an overflow-tube (Fig. 1). The overflow level was set at 25 cm above the sole of the foot. The displaced water was spilled into a can. The water was collected until the drop rate fell below one drop per second, after which the water volume in the can was carefully measured by weighing (average of three measurements, accuracy ± 1 g). The weight was converted to volume assuming that 1 g is equal to 1 ml of water. The difference in the volume of displaced water was regarded to express the actual difference in volume between the two legs.[4] The temperature of water was 30 °C and the room temperature 22–25 °C. In the patients with skin ulceration the water was mixed with germicidal soap.

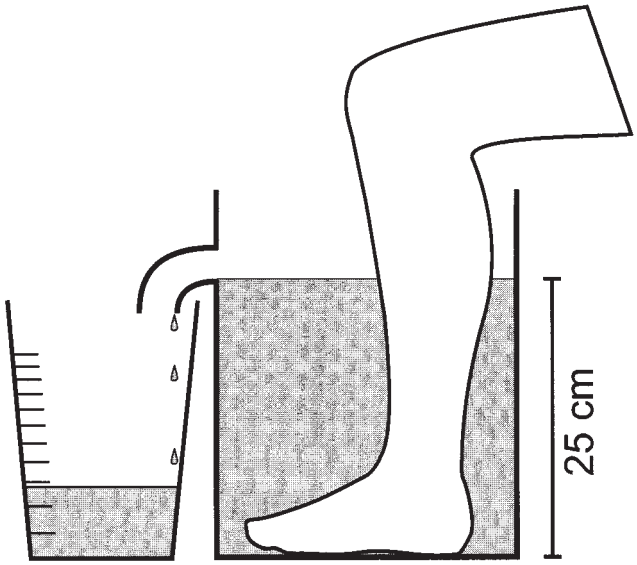

Fig. 1. Schematic illustration of the technical set-up for water displacement volumetry (WDV).

Colour duplex ultrasound (CDU)

CDU combines B-mode tissue and colour-flow imaging (Doppler) with spectral blood flow analysis by Doppler ultrasound. All CDU examinations were performed by one specialised angiologist (MD) using a Vingmed System Five ultrasound scanner (Vingmed Sound A/S, Horten, Norway) with a 5 MHz linear array probe. The common femoral, superficial femoral and deep femoral veins were examined with the patient in supine position.[5,6] The popliteal vein and major calf veins were scanned with the patient sitting on an examination table with the legs tilted downwards.[5] Venous imaging included both longitudinal and transverse planes. The diagnosis of venous thrombosis was based on a combination of the following findings: (1) absence or defective colour flow in the vein during distal manual compression and (2) lack of or incomplete compressibility of the major veins.[5,7]

Air plethysmography

For venous occlusion plethysmography (VOP) an air plethysmograph (Macrolab, Stranden) was used to exclude venous outflow obstruction caused by DVT. The subjects were recumbent for 15–20 minutes prior to the measurements and the lower limbs were supported by cushions under the thigh and foot with the calf slightly above the level of the sternum. The venous occlusion and recording cuffs were applied proximally to the patella and at the calf, respectively. Their width

was approximately 70% of the limb's circumference. The pressure in the recording cuff was 6 mmHg. An occlusive cuff pressure of 50 mmHg was maintained for one minute. This permits uninhibited arterial flow into the limb while venous outflow is compromised, thus resulting in an increased leg volume. On decompression of the thigh cuff after one minute, leg volume decreases rapidly if venous outflow from the lower limb is unobstructed. The degree of decline of the plethysmographic curve on release of the thigh cuff is a measure of "venous emptying" and indicates whether the patient has any functionally significant venous obstruction.[8,9]

Blood sampling and examination

Among the chemical and haematological blood tests which were done, several were indicative for possible causes of generalised oedema formation. Blood from antecubital veins was collected for analysis of haemoglobin (Hb), haematocrit (Hct), red cell count (RBC), thrombocyte count (Trc), white cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (SR), sodium (Na), potassium (K), calcium (Ca), chloride (Cl), creatinine, urea, uric acid, creatine kinase (CK), glucose, cholesterol, triglyceride, albumin, total protein, alanine-amino transferase (ALT), aspartate-amino transferase (AST), lactate dehydrogenase (LDH), alkaline phosphatases (ALP), gamma-glutamyl transpeptidase (γ-GT), bilirubin, α-amylase, normotest (NT).

Statistics

Wilcoxon matched-pairs signed-ranks test and Student's *t*-test for independent samples were used for comparing changes in ABI, ASP and leg volume. The results were presented as mean $\pm$ standard deviation (S.D.), with $p<0.05$ chosen as the level of statistical significance. Medians are presented with ranges in parentheses.

Results

The median ASP was 15 mmHg (15–100) and median ABI was 0.28 (0.09–0.6) in the limbs *with* CLI, compared to 150 mmHg (60–220) and 0.94 (0.54–1.0) in the limbs *without* CLI, respectively (Table 2). In 6 limbs with CLI, ultrasound Doppler signals could not be detected.

Table 2. Median ankle systolic pressure (ASP) and ankle–brachial index (ABI) in limbs with and without CLI.

	CLI	No CLI
ASP (mmHg)	15 (15–100)	150 (60–220)
ABI	0.28 (0.09–0.6)	0.94 (0.54–1.0)

Table 3. Water displacement volume (WDV) measurements of limbs with and without CLI.

	CLI	No CLI	Volume difference (%)	Significance*
Volume (ml)	1279 ± 325	1179 ± 298	9	$p<0.002$

* Wilcoxon signed-rank test.

The mean volume of the legs *with* CLI was 1279 ± 325 ml. In those *without* CLI mean volume was 1179 ± 298 ml, which is a statistically significant difference of 9% ($p<0.002$, Wilcoxon signed-ranks test) (Table 3). None of the patients had functionally significant DVT as assessed by CDU and VOP.

Haematological analysis showed no signs of pathological liver, pancreas or kidney function. Cholesterol, lipid parameters and electrolytes were within the reference intervals. In addition, infection parameters were normal. Mean plasma albumin concentration was 28.5 ± 6.6 g/l which was significantly lower than the reference intervals.

Discussion

The pathophysiological significance of oedema in CLI has not been clarified. The oedema causes increased distance between the cells due to distensibility of the interstitial space.[2] Furthermore, it disturbs "tissue respiration", leading to reduced oxygen delivery and accumulation of metabolic end products.[10] In other words, interstitial oedema may aggravate hypoxia in already critically ischaemic peripheral tissues.

Since the magnitude of this oedema is most likely related to the severity of its pathophysiological consequences, it seemed relevant to quantify it. The present finding of a mean volume difference of 9% between limbs with CLI and contralateral sides confirms that this oedema is considerable. However, one may speculate whether the volume difference only expresses oedema formation. Most of the patients relieve their

symptoms by lowering the painful leg. This elevates venous pressure, and increases venous volume, since distension of the veins may follow long-lasting increase in transmural pressure.[11] Theoretically, this might partially explain the measured difference in leg volume between limbs with and without CLI. However, none of the patients in this study had obvious venous insufficiency. Furthermore, the leg volumes were measured while the patients were sitting with *both* legs in the dependent position. Because both limbs were measured in the same position, leg volume differences between limbs with CLI and contralateral side are probably not due to an increased intravascular blood volume. Besides, these patients had clinical signs of "pitting" oedema, which is defined as the accumulation of excessive fluid in the extracellular, interstitial space. Therefore, the difference in volume represents most probably the magnitude of oedema.

Although application of an elastic stocking probably limits oedema formation,[12] it may compromise the very marginal arterial- and microcirculation. However, the effect of this measure, to our knowledge, has not yet been systematically investigated.

Other methods than WDV[4] have been used to measure limb volume: (1) disc model methods,[13] (2) frustum method[13] and (3) infrared optoelectronic volumetry.[14] All three methods are based on the assumption that the leg approximates in shape to a truncated cone. Both disc and frustum techniques have the advantage of requiring minimal technology and are easy to perform, both in dependent and supine positions.[13] Infrared optoelectronic is an expensive technique which is not yet well established in clinical research.[14] Furthermore, this method allows measurement of limb volume in the horizontal position, excluding the foot.[15,16] However, since the oedema in the patients with CLI is clinically mainly localised to the ankle and foot, the frustum, disc and infrared optoelectronic volumetry methods are not suitable in these patients.

The WDV is an accurate method and continues to be used as the "gold standard" for the measurement of the leg volume.[4,15,16] Furthermore, it has the advantage of being a direct method, requiring only a single volume measurement.[4,15] By using WDV we avoided elevation of the limb to the horizontal position during measurement, which generally agrees with the patient's wish to lower the limb with CLI to relieve rest pain.[1] In patients with open wounds on the leg or foot we added soft germicidal soap to the water. The equipment for WDV is easily disinfected.[15,16] In our experience WDV is a reliable and simple method causing little discomfort to the patients.

One of the most likely causes of unilateral limb oedema is DVT, specially in patients with low peripheral arterial flow where venous blood flow is compromised. However, functionally significant DVT could be excluded as a causative factor. Since local infection also might have been another cause of unilateral foot oedema, these patients had been excluded from our study. The radiological diagnosis of DVT in the lower limbs has traditionally been made by phlebography.[17] Non-ionic, low osmolar contrast media have fewer side-effects and complications;[18,19] however, a considerable amount of contrast medium is still required with long leg films to increase the sensitivity and specificity of the method.[20] These agents should preferably be avoided in patients with generalised atherosclerosis, which also often affects the arterial blood supply to the kidneys.

CDU is today a well-established method in the diagnosis of proximal thrombosis in symptomatic patients.[21,22] However, the method is less accurate in detecting distal thrombi.[17,23] This disadvantage was less relevant in the present investigation where the main question was whether a *major* DVT could be detected as the cause of oedema formation. In the present context VOP is a good method to assess venous outflow in the lower limb.[7,8] Although plethysmography does not have a generally high sensitivity and specificity in diagnosing DVT,[24] it is a reliable method to exclude functionally significant venous outflow obstructions.[17] "Functionally significant" means a venous obstruction of a magnitude which causes increased distal venous pressure which eventually may lead to oedema formation. In previous investigations the combination of CDU and VOP have met the criteria for screening test of DVT.[17,23,24]

The mean plasma albumin concentration in our patients was significantly lower than the reference intervals. The majority of patients with CLI do not live in an institution but at home,[25] and they often are not able to provide adequate nutrition. Malnutrition is probably the major cause of low serum albumin concentration in patients with CLI.[26] However, low plasma albumin levels can be excluded as a cause of *unilateral* oedema. On the other hand, it may contribute to reducing the safety margin against general oedema formation.

The present finding of a mean volume difference of 9% between limbs with CLI and the contralateral side confirms that this oedema is considerable. Theoretically impaired lymph flow may be a cause of unilateral lower limb oedema. Since none of these patients had undergone groin surgery, there were no obvious reasons why lymph vessels should have been traumatised. In addition, neither oedema nor increased

tissue pressure will necessarily decrease lymph flow.[27] Previous research has shown the importance of intracapillary leukocyte "sludging" during low flow states of CLI. A complex cascade of reactions, where the formation of oxygen-free radicals plays a role, will cause a local inflammatory-like process with increased capillary permeability, of which oedema formation is one of the local symptoms.[28] Therefore the aetiology of oedema formation in patients with CLI is most likely multifactorial. Disturbance in transcapillary fluid transport is probably an important factor, and further investigations to elucidate this aspect are in progress.

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Accepted 23 November 1998