Atrophie blanche

ATROPHIE BLANCHE

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Wie nooit heeft geleden, heeft nimmer geleefd.
Wie nooit zich vergiste, heeft nimmer gestreefd.
Wie nooit heeft geweend, heeft geen vreugd' als hij lacht.
Wie nooit heeft getwijfeld, heeft nooit ernstig gedacht.

Aan mijn moeder en Michel
Ter nagedachtenis aan mijn vader

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

Chronic Venous Insufficiency (CVI) of the legs is a complex of symptoms, caused by continuously elevated intravenous pressure (due to upright position).
The increased venous pressure in the legs of patients with CVI is in the majority of the cases the result of venous reflux. There are several causes for venous reflux:

1) primary varicosis, including perforator incompetence. According to Feuerstein about 56% of the venous leg ulcers is the result of superficial venous insufficiency (both primary varicosis and perforator incompetence).[1]
2) post-thrombotic damage in the deep veins. As result of deep venous thrombosis (DVT) the valves of the deep veins are destroyed. Sometimes there is even residual venous obstruction. Post-thrombotic damage forms in about 44% the cause for venous leg ulcers.[1]
3) in less than 1% other disorders, such as congenital valvular incompetence, are the cause of CVI.

CVI leads to the development of skin abnormalities, often resulting in chronic and recurrent, sometimes painful leg ulcers. Because of these skin disorders and leg ulcers, patients often visit the dermatologist. Leg ulceration and recurrent leg ulcers form a daily problem for both patient and doctor.[2]
Patients with CVI form a considerable part of the patients seen by the dermatologist. In the university hospital of Maastricht 16% of the consultancies concern a phlebological disorder. In the general population the prevalence of varicose veins is estimated to be between 15 and 55%.[3-5] In the study of Widmer varicosis was seen in 55%.[5] Major varicosis (trunk varicosis) was seen in about 10%, which is three times less than reticular veins are seen. It has been estimated that CVI will develop in almost 50% of patients with major varicose veins.[6] CVI (including skin changes) was seen in 6% in the general population in the study of Widmer. The estimated prevalence of CVI by Callam is 2 to 7%.[7] It is unclear which percentage of CVI is caused by post-thrombotic damage. In a study of Nicolaides 35% of the patients with CVI had deep venous insufficiency.[8] The prevalence of leg ulcers is estimated around 1.2%.[9,10]
In this introduction I will briefly summarise the current knowledge on CVI, relevant for this thesis.

CHRONIC VENOUS INSUFFICIENCY

Untreated CVI leads to a sequence of microcirculatory changes of the skin that result in the clinical sequelae of oedema, corona phlebectatica, hyperpigmentation ("dermatite jaune d'ocre"), dermato- et liposclerosis, atrophie blanche and finally ulcers [figure 1].[2,6,11] Damage or incompetence of the venous valves and subsequently reflux in the superficial, deep or perforating system is the most important cause of CVI.[12] Venous reflux leads to a relatively insufficient pump function of the calf muscle and an increase of the walking venous pressure at the ankle. This increased walking venous pressure induces dilatation and a tortuous appearance of the capillaries, leading to capillary leakage and oedema formation.

From this point on functional changes of the microcirculation induce many pathological alterations leading to the clinical syndrome known as CVI.[13]

FIGURE 1
Clinical aspects of CVI.

An important clinical classification for severeness of CVI is made by Widmer in 1981 [table 1].[5] The Widmer classification is based mainly on clinical symptoms and is still the most widely used because of its simplicity. Also in daily practice most dermatologists categorise all their patients with venous complaints.

TABLE 1
Widmer classification[5] in symptoms of CVI

Class	Symptoms
I	Corona phlebectatica paraplantaris Oedema (sub-clinical)
II	Oedema (clinical) Pigment disorders Dermato- et liposclerosis Atrophie Blanche
III	Leg ulcer Leg ulcer in the past

A new classification, however, was developed because the Widmer classification and other classifications were not precise enough, resulting in a very large inter patient variation in one group, which makes it very difficult to compare certain groups of patients. Especially the haemodynamic differences in these groups can be very large. In 1995 this new, more thorough classification called CEAP (or Hawaii) classification has been designed [table 2].[14] The new classification categorises patients with venous diseases on the basis of different parameters: Clinical, Etiological, Anatomical and Pathological. It must be realised, however, that patients should be reclassified during time, for instance after treatment. In daily practice this classification is very time consuming for both the doctor and patient due to all the investigations, and is therefore not very usefull. The most important disadvantage of the CEAP classification is, however, that also this classification is not complete, because haemodynamic disturbances are not classified. As result, for instance, a patient, which is developing a post-thrombotic syndrome, is not categorised correctly.
Besides that it is important to classify a patient, it is important to investigate the severeness of the patients disease by clinical symptoms, anatomical and functional changes of the venous system. Therefore it is necessary to elucidate underlying abnormalities in the venous system and to determine the severity of CVI by quantitative measurements.
Investigative techniques can be divided into anatomical investigations (duplex and phlebography) and functional (plethysmography, duplex and direct pressure measurements) investigations. Direct venous pressure measurements in a large group of patients show a linear relation between ulceration and walking venous pressure.[8] An increased incidence of ulcers is associated with an increase in walking venous pressure irrespective of whether the venous problem was the result of superficial or deep venous disease.[8]
During the past two decades, new non-invasive techniques have been developed to study microcirculation. The techniques most often used today are laser Doppler fluxmetry, transcutaneous oxygen measurement (TcPO2) and capillary microscopy.

MICROCIRCULATION

All clinical signs of CVI, including the leg ulcer and atrophie blanche, are the result of the alterations of the skin microcirculation induced by the walking venous hypertension. Studying the microcirculation is therefore of great importance for understanding the clinical syndrome of CVI. In the past decades several non-invasive instruments have become available to study the microcirculation of the skin. Non-invasive techniques for investigating microcirculation are capillary microscopy (direct)[15,16], transcutaneous oxygen tension ($TcPO_2$)[17,18], laser doppler flux[19] measurements and different forms of plethysmography.

TABLE 2: CEAP classification[14]

Clinical classification
0 No visible or palpable signs of venous disease
1 Teleangiectatic or reticular veins
2 Varicose veins
3 Oedema
4 Skin changes ascribed to venous disease
5 Skin changes as defined with healed ulcers
6 Skin changes as defined without healed ulcers (active ulcers)
Etiological classification
Congenital
Primary - with undetermined cause
Secondary: - post thrombotic
- post traumatic
- other
Anatomical classification
Superficial veins
1 Teleangiectases/reticular veins
Long saphenous vein
2 - Above the knee
3 - Below the knee
4 Short saphenous vein
5 Non-saphenous vein
Deep veins
6 Inferior vena cava
Iliac vein
7 - Common
8 - Internal
9 - External
10 Pelvic vein
Femoral vein
11 - Common
12 - Deep
13 - Superficial
14 Popliteal vein
15 Crural vein- anterior tibial, posterior tibial, peroneal
16 Muscular vein- gastrocnemical, soleus, other
Perforating veins
17 Thigh vein
18 Calf vein
Pathophysiological
Reflux
Obstruction

The microcirculation of the skin can be divided into a nutritional and a thermoregulatory part. The laser doppler fluxmetry measures mainly the flux of the thermoregulatory vessels (85%) and in lesser degree the nutritional capillaries (15%).[20,21] TcPO2 probably reflects for a greater part the function of the nutritive skin capillaries.[20,21] With capillary microscopy capillaries in the skin are seen, which probably represent mainly the nutritional status of a certain area.

A number of abnormalities in relation to microcirculation have been discussed in the literature in patients with CVI.

- Changes in capillaries. With capillary microscopy Fagrell observed dilated, tortuous and elongated capillaries in the skin of the medial ankle region area in patients with CVI.[22] Capillary density seems to be largely unchanged in skin with oedema, cyanosis and hyperpigmentation, but is reduced in patients with more severe CVI. Especially in atrophie blanche a strongly reduced number of capillaries is counted, even reaching zero.[23]

Patients with mild to severe CVI, including morphological changes, but without a reduction in the number of capillaries, already have a reduced $TcPO_2$ values. A decrease in $TcPO_2$ values can be correlated with a reduction in capillary density. In the centre of atrophie blanche values may reach zero.[23]

- Changes in permeability. Around the capillaries halo's are visible, which consist of oedema, polysaccharides, haemosiderine and fibrin.[24] The diameter of the halo is smaller in healthy controls than in patients with severe CVI.[25,26] Transcapillary diffusion can be measured with sodium-fluorescein. An increased permeability is seen in mild CVI, not in severe CVI.[25,26] This might be explained by a fibrin cuff around capillaries in patients with severe CVI.

- Increased fibrin formation. Fibrin accumulation (perivascular cuffs) in tissue close to ulcers has been demonstrated by several authors. The theory of fibrin cuffs is from Browse and Burnand.[27] They suggest that as a result of continuously increased venous pressure, capillaries will dilate, resulting in increased leakage of fibrinogen. Around the vessels this will be converted into fibrin, forming a cuff around the capillaries. The function of these cuffs is still unclear. Some authors find a decreased diffusion of oxygen, while others did not measure differences in oxygen tension in lesions with or without fibrin cuffs.[28-30]

The microvascular skin flux (the concentration of moving blood cells multiplied by the magnitude of the median velocity) is measured by laser doppler fluxmetry. Laser doppler flux is increased in patients with CVI.[31,32] Flux is already increased when macroscopical changes of the skin are minimal.[33] Both a decreased vasoconstriction response as an unchanged response in patients with CVI have been described.[31,32] The same is true for the pattern of vasomotion. Patients with mild to severe CVI showed no alterations in pulsatile flux waves, low-frequency vasomotion and high-frequency waves, whereas vasomotion frequency and amplitude were augmented in patients with severe CVI.[34]

Coleridge Smith suggested an accumulation of white blood cells in capillaries in the legs of patients with CVI.[35] An increased ratio of red and white blood cells was found in the long saphenous vein. Trapping of white cells induces activation of

these cells, resulting in degranulation and release of oxygen radicals and proteolytic enzymes.
Recently, in 1993, a hypothesis for the pathogenesis of venous ulceration was suggested by Falanga en Eaglstein.[36] They suggest that venous hypertension induces microtrauma of the endothelial cells, resulting in an increased capillary permeability. As a result macromolecules, such as fibrin and other macroglobulins, leak into the dermis, trapping growth factors, contributing to slow healing ulcers.
Another interesting theory is suggested by Bollinger *et al.*[37], because for this theory both histological and capillary microscopical evidences are found. In this theory microthrombi develop as a result of change in blood flow in capillaries. With sodium-fluorescein capillary microscopy, a decreased flow is observed in atrophie blanche lesions. The sodium reaches the centre of a lesion much later in atrophie blanche lesion than in healthy skin.[38] Also with electron microscopy and light microscopy microthrombi could be found.[39]
Whether these changes in capillaries are merely a result of venous hypertension or whether they play an important role in aetiology is still unclear.
Enhanced fibrin formation and decreased fibrinolytic response might play a role in patients with CVI, which could stimulate locally the formation of microthrombi.
Recently Falanga *et al.* found increased values of fibrin degradation products in plasma of patients with CVI.[40] An increased total fibrin-related antigen (p=0.04) and increased D-dimer levels (p=0.006), a degradation product of cross-linked fibrin was found in patients with CVI with and without ulcers compared with 15 healthy controls. Fibrinogen degradation products were in the normal range. Patients which recently had undergone surgical or invasive procedures, or patients with cellulitis or recent infection were excluded. It was therefore suggested that patients with CVI have an increased production of fibrin.
There is some evidence for a decreased fibrinolytic activity in patients with CVI. Increased levels of plasminogen activator inhibitor-1 (PAI-1) antigen were found in a double blind study in 20 patients with CVI (venous leg ulcers) compared with healthy controls.[41] Increased levels of PAI-1 activity can be a sign of diminished fibrinolysis. Also Veraart *et al.* found increased values of PAI-1 activity in patients with Klinefelter syndrome complicated by skin changes (including atrophie blanche and leg ulcers), clinically indistinguishable from the lesions seen in CVI, but without objective valve disturbances of the venous circulation.[42]

TREATMENT OF CVI

Compression therapy is widely used in the treatment of all kinds of phlebological diseases. Because in daily practice it has been proved to be effective for venous leg ulceration, it has been generally accepted as first choice for treatment. It has been demonstrated in only a few studies that under normal ambulant conditions, compression therapy is superior in treating venous leg ulcers compared with treating without compression therapy.[43,44] Although practised by many doctors, there are hardly any 'evidenced based' data available on the favourable effects of

this treatment in CVI.[45-47] It is important to realise that before compression treatment is given a thorough analysis of the patient's venous disorder should be made. If possible, restore of the venous haemodynamics with adequate surgery and/or flebectomy or sclerocompression therapy should be performed. If these treatments are not a serious option or even contraindicated for treatment of severe CVI, compression therapy should be given. Compression therapy is of course only indicated when arterial diseases have been ruled out (ankle/arm index > 0.8).
After healing of venous leg ulcers, recurrence rates can be reduced dramatically if compression therapy is persisted. After an average of 30 months wearing class III stockings, recurrence rates were 16% in the compliant group and 100% in the non-compliant group.[46]
The importance of compression therapy in the prophylaxis and treatment of deep venous thrombosis (DVT) is less clear. Compression therapy in the combination with low molecular weight heparins (LMWH) seems to have a synergistic effect in preventing DVT.[48] It has been suggested that compression therapy can be effective in the prevention of acute complications after a DVT. Partsch *et al.* treated a group of patients with acute DVT by early compression therapy and ambulation, beside standard anticoagulant therapy.[49] Concerning the occurrence of pulmonary embolism, the group performed no worse than the standard treatment with bed rest and anticoagulant therapy. Compression therapy prevents the development of late complications, such as the postthrombotic syndrome.[50,51] Recently a study of Brandjes showed a decrease in incidence of the postthrombotic syndrome in more than 50% in patients wearing compression stockings class III for 2 years after a DVT compared with patients without stockings.[51]

DEEP VENOUS THROMBOSIS

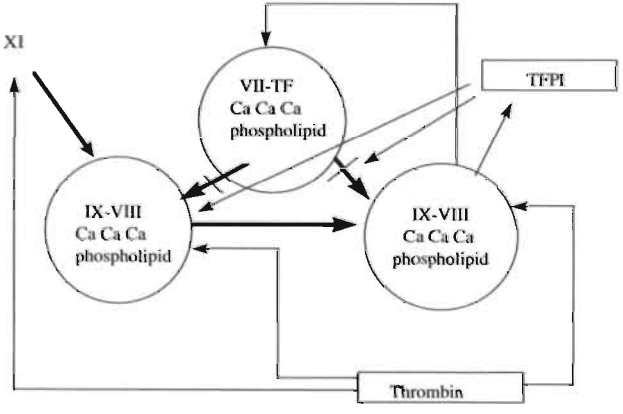
DVT is often seen in clinical practice and is associated with significant morbidity and mortality. There is a clear relation between DVT, resulting in the postthrombotic syndrome and the symptoms of CVI, like atrophie blanche, dermato- et liposclerosis and venous leg ulcers. In the pathogenesis of DVT disturbances of haemostasis are important.

HAEMOSTASIS

Over a century ago Virchow summed up the conditions leading to a DVT as hypercoagulability, damage to the vein wall and slowing down of the venous blood flow. These principles are still accepted, but extensive research has revealed a complex system of factors that induce or inhibit the formation of a haemostatic plug.
The haemostatic system is the result of interaction between platelets, vascular endothelial cells, plasma coagulation proteins, fibrinolysis and inhibitor systems. The haemostatic system is regulated by a balanced system of activators and

inhibitors. Thrombin is the central enzyme in haemostasis and thrombosis.[52] Thrombin acts at the level of the plasma, the platelet and the vessel wall. It is one of the most potent in vivo platelets activators. Activated platelets on the other hand are essential in the process of abundant thrombin generation.
After destruction or traumatisation of the vessel wall a chain reaction is induced which finally results in the formation of thrombin and fibrin. Three main mechanisms can be divided. The first reaction after traumatisation of the vessel wall is vasoconstriction and formation of a procoagulant subendothelium. The second mechanism which can be seen is the adhesion and aggregation of platelets. The third mechanism is the formation and polymerisation of fibrin.
Damage of the vessel wall leads to exposure of tissue factor (TF) to the plasma proteins.[53] TF binds factor VII. The TF-factor VII complex activates factor X into factor Xa. The conversion of the TF-factor VII complex into the TF-factor VIIa complex is catalysed by factor Xa, with a much higher enzymatic activity.[54] In addition, the TF-factor VIIa complex activates factor IX, which in turn can also activate factor X into Xa [figure 1].[55,56]
Factor Xa alone converts prothrombin into thrombin at a very low level (less than 0.1% of the velocity of full prothrombinase). Small amounts of thrombin thus generated produce feedback reactions: activation of factor V into Va, of factor VIII into VIIIa and activation of platelets.[57,58]

FIGURE 2
Schedule of coagulation.



TF = tissue factor
TFPI = tissue factor plasminogen inhibitor
VII, VIII and IX = coagulation factor VII, VIII and IX

Within seconds after traumatisation, platelets adhere to adhesive proteins in the subendothelium, such as collagen, fibronectin and laminin. After adhesion a chain of reaction is induced: changing in shape of platelets from a smooth disc to a irregular sphere with pseudopods and the release of ADP, ATP, PF4, vWf and TxA_2. The point of no return is the activation of the fibrinogen receptor on the surface of the platelets, the glycoprotein IIb-IIIa. After activation glycoprotein IIb-IIIa binds fibrinogen resulting in the formation of plateletaggregates.
Together with the activation of glycoprotein IIb-IIIa, procoagulant negatively charged phospholipids from the inner membrane of the platelets are exposed, which is the so-called 'flip-flop' of the membrane.[59]
Factor Va binds to these negatively charged phospholipids. After binding, factor Va serves as a platelet binding site for factor Xa. For a rapid, massive generation of thrombin the full complex Va-Xa-phospholipids (prothrombinase) is required.
The extensiveness of the clot formation is related to the location and the kind of trauma. Thrombin plays a central role in the process and the amount of thrombin is closely related to
-the release reaction of platelets and their flip-flop mechanism
- activation of factor V and factor VIII
- formation and cross-linking of fibrin
- activation of factor XI
- activation of protein C pathway
- inhibiting fibrinolysis by thrombin activated fibrinolysis inhibitor (TAFI)

INHIBITORY MECHANISMS

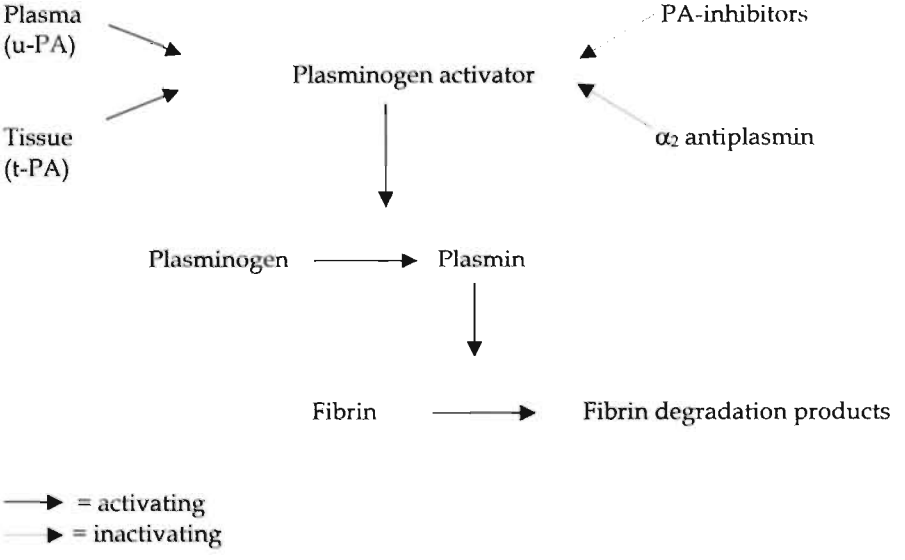
Activation of platelets and coagulation are closely related processes. Over-activation increases the risk of thrombosis. There are several mechanisms contributing to the balance between thrombin formation and inactivation, by which the process of coagulation stays localised. Two important mechanisms occurs via tissue factor pathway inhibitor (TFPI) and activated protein C (APC).
Thrombomodulin is a membrane glycoprotein, present at the surface of intact endothelium. Thrombin can bind to thrombomodulin and so looses its procoagulant properties and activates protein C. After activation of protein C a complex is formed with its cofactor protein S. This complex neutralises free activated factors V and VIII, [60,61] damping down the coagulation and thrombin formation (in this way inactivating both tenase and prothrombinase) and it activates fibrinolysis by inhibiting PAI-1. The importance of these inhibitor mechanisms is seen in patients with a deficiency of antithrombin, protein C, protein S or with APC resistance, resulting in increased thrombotic risk.[62]
TFPI inactivates the coagulation initiated by the TF-factor VIIa complex. TFPI binds to first to factor Xa.[63] This complex inhibits TF-factor VIIa complex. This mechanism ensures that tissue factor-induced factor X activation will stop as soon as sufficient factor X is present. The plasma concentration of TFPI is very low but a substantial amount is present in endothelial cells and can be released, for instance, by the cell membrane binding of heparin.

Thrombin, once formed, is inactivated by plasma protease inhibitors (antithrombins).[64] Antithrombin is the most important, contributing for 64% of total antithrombin activity, α2-macroglobuline accounts for 23% and the remaining 13% is taken care of by other antiproteases (mainly α1-antitrypsin).[65]

FIBRINOLYSIS

The fibrinolytic system compromises an inactive pro-enzyme, plasminogen, which can be converted to the active enzyme, plasmin, which degrades fibrin into soluble fibrin degradation products [figure 2]. Two immunologically distinct physiological plasminogen activators have been identified in the blood: tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). t-PA is released from endothelial cells and u-PA from monocytes and leucocytes.[66] Inhibition of the fibrinolytic system may occur either at the level of the plasminogen activators, by specific activator inhibitors (PAI-1, PAI-2 and TAFI), or at the level of plasmin by α_2-antiplasmin.

FIGURE 3
Schedule of fibrinolysis.



DEEP VENOUS THROMBOSIS

In about 50% of patients with leg ulcers as symptom of CVI, a history of DVT is seen.[67] However, it must be emphasised that a diagnosis of DVT must be based on objective diagnostic methods and not solely on clinical grounds.
The prevalence of DVT is estimated to be 1-3 per 1000 in the general population.[68,69] Incidence of DVT is increasing with age. With the introduction of contrast phlebography it became apparent that in only 30% of the patients with clinically suspected DVT, the diagnosis could be confirmed by phlebography.[70,71] Phlebography has been the gold standard for the diagnosis of DVT for a long time. Phlebography is an invasive, painful technique with a small risk of contrast media related complications.[72,73] The disadvantages of this investigation should be considered.
With the introduction of compression ultrasonography (or echo) and duplex scanning excellent alternatives for phlebography have been found.[74] The accuracy of compression ultrasonography and duplex scanning is especially high in patients with a first period of suspected DVT of the proximal veins (vena poplitea and higher).[75,76] The accuracy of duplex scanning in the diagnosis of proximal DVT is comparable to ultrasonography.
Ultrasonography is the first choice for the diagnosis of DVT in patients with a first symptomatic episode of proximal DVT. There are, however, several limits for the use of ultrasonography. 1) In patients with isolated pelvic vein thrombosis echo can be negative. In case of a high suspect pelvic vein thrombosis, venography should be performed. 2) For the screening of asymptomatic population with a high risk for DVT (for instance after hipsurgery), echo is not qualified. 3) The sensitivity of calf vein thrombosis with echo is considerable less than for proximal vein thrombosis. The spontaneous development of a calf vein thrombosis is unknown. Probably about 10-20% of calf vein thrombosis will extend to proximal. The necessity for treatment of calf vein thrombosis is therefore not clear. It has been suggested that only distal DVT extending to proximal should be treated and that DVT limited to the calf should not be treated, because the risk of pulmonary embolism is negligible.[75,77] A recent study, however, showed that the risk of post thrombotic syndrome after distal DVT is considerable less than after more proximal DVT, but should not be neglected, which causes concern about not diagnosing and not treating patients with distal DVT.[78] 4) The usefulness of echo in the diagnosis of recurrent DVT has been questioned, because normalisation occurs in only around 50% during the first year.[79] The use of the criterion of compression is of limited value for recurrent DVT diagnostic management. At this moment D-dimer (degeneration products of cross linked fibrin) has been studied as potential aid in the diagnostic management of DVT. D-dimer testing can not be used as the only diagnostic tool to detect thrombosis because of its low specificity. However, it could be a valuable additional test to exclude a new thromboembolic process in the first period of suspected DVT as well as in recurrent signs of new DVT.[80,81]

The pathogenesis of DVT is complex. The risk for the development of DVT is associated with a number of clinical conditions (surgical procedure, immobilisation, pregnancy, trauma and the use of oral contraceptives), acquired risk factors (malignancy, age, antiphospholipid antibodies and bowel diseases (Crohn's disease and colitis ulcerosa) and congenital risk factors (antithrombin, protein C and S deficiency, factor V Leiden mutation, prothrombin mutation, hyperhomocysteinaemia, and dysfibrinogenaemia.
It is very likely that in the individual patient a combination of factors finally result in symptomatic thrombosis. Interaction of several factors, such as the combination of factor V Leiden mutation and the use of oral contraceptives, are known for the increased risk in developing DVT.[82,83] It is therefore important to screen a patient for thrombophilia so that adequate prophylactic and therapeutic recommendations can be given.
The prevalence of the main hereditary factors associated with an increased risk for thrombosis processes varies in different patient groups. A summary of the most important hereditary factors of which the relation with DVT is proven, is given in table 3.
A number of other abnormalities have been postulated, which might also increase the risk for developing DVT. They are mentioned in table 4.

TABLE 3
Prevalence of main established hereditary risk factors for DVT [84]

	Normal population	Thrombosis population
Factor V Leiden mutation	5%	20%
Protein C deficiency	0.3%	3%
Protein S deficiency	unknown	1.5%
Antithrombin deficiency	0.04%	1%
Prothrombin mutation*	1%	7%
Hyperhomocysteinaemia*	11.5%	25%
Dysfibrinogenaemia	unknown	unknown

* also associated with arterial thrombosis

THROMBOPHILIA

Thrombophilia can be defined as "the familial or acquired abnormalities of the haemostatic mechanism likely to predispose to thrombosis".[85] Thrombosis can occur spontaneously in the absence of a recognised risk factor. It is difficult to find out whether thrombosis occur spontaneously or that the patients has thrombophilia. Clinical signs for thrombophilia include venous thrombosis at

young age, recurrent venous thrombosis, family history of venous thrombosis, venous thrombosis at unusual sites, recurrent fetal loss, coumarin induced skin necrosis, neonatal purpura fulminans and heparin resistance. It is advised to screen every patient with DVT for thrombophilia, if they suffer thrombosis before the age of 45, or when suffered from the above mentioned clinical signs.[86] Thrombophilia tests should be performed at distance of an acute episode and whenever possible in nonanticoagulant, nonpregnant, and in the nontaking oral contraceptive pill patient.[62]

TABLE 4
Potential factors with increased risk for DVT

Potential factors predisposing to thrombosis
* Thrombomodulin mutations
* Increased levels of factor VIII
* Plasminogen deficiency
* Heparin cofactor II deficiency
* ß2 glycoprotein I deficiency
* Increased levels of histidin-rich glycoproteine
* Tissue factor pathway inhibitor (TFPI) deficiency
* Thrombin-activated fibrinolysis inhibitor (TAFI) excess

FACTOR V LEIDEN

Factor V Leiden is a relatively new known risk factor for DVT, which seems to play an important role. The first reports about the activated protein C (APC) resistance came from Dahlbäck in 1993.[87] APC resistance appeared to be a characteristic of selected patients with venous thromboembolism, particularly those who had positive family histories and were relatively young. In rapid succession, studies directed by Bertina[88] and Dahlbäck[87] as well as the Leiden thrombophilia study[89], found that the cofactor responsible for resistance to APC, is a previously unrecognised form of coagulation factor V. This resistance was associated with a gene defect, called factor V Leiden mutation.
Factor V Leiden mutation is a specific point mutation in which adenine is substituted for guanine at nucleotide 1691 in the gene coding for coagulation factor V. Factor V Leiden mutation alters APC cleavage site of coagulation factor V and produces a mutant molecule that cannot be properly inactivated by APC.
APC resistance accounts for about 20% of DVT, and for 50% of familial venous thrombosis.[88,90,91] Factor V Leiden therefore plays an important role in the pathogenesis of DVT and might therefore also be important in the pathogenesis of CVI.

AIMS OF THE THESIS

1) Recurrent leg ulcers are often seen in patients with CVI in daily practice. What is the prevalence of atrophie blanche in patients with leg ulcers and are recurrent leg ulcers seen more often in patients with CVI and atrophie blanche than in patients with CVI without atrophie blanche? (Chapter 3)
2) Microcirculation in patients with CVI is disturbed. Microcirculation can be studied with laser Doppler perfusion imager, transcutaneous oxygen measurements and capillary microscopy. Is there a difference in flux, measured with laser Doppler perfusion imager, in atrophie blanche lesions and healthy controls? What is the effect of artificially induced venous hypertension on the flux in atrophie blanche, and on transcutaneous oxygen values. Is there a different reaction pattern on venous hypertension in patients with CVI with and without atrophie blanche and healthy controls? What is the effect of venous hypertension in capillaries in patients with CVI? Can changes in capillary blood cell velocity be determined with conventional capillary microscopy? Is the effect of venous hypertension the same in capillaries in CVI patients as in nailfolds of healthy controls? Are standstills in capillaries visible during venous hypertension, and is there a difference between several levels of venous hypertension? (Chapter 4 and 5)
3) A lot of patients with deep venous thrombosis show factor V Leiden mutation. A history of deep venous thrombosis is often seen in patients with venous leg ulcers. What is the prevalence of factor V Leiden mutation in patients with venous leg ulcers? Is factor V Leiden mutation seen more often in patients with recurrent leg ulcers, atrophie blanche or dermato- et liposclerosis ?(Chapter 6)
4) Microthrombi are suggested to play an important role in the pathogenesis of atrophie blanche. Several anticoagulants are suggested in the treatment of atrophie blanche. What is the effect of low molecular weight heparins on the microcirculation in atrophie blanche, measured by laser Doppler perfusion imager, transcutaneous oxygen values and capillary microscopy? (Chapter 7)

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CHAPTER 2

ATROPHIE BLANCHE, A REVIEW

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INTRODUCTION

Atrophie blanche (AB) is a common skin disorder (prevalence 1-5%). It is predominantly localised in the lower leg and characterised by a distinct clinical morphologic appearance and the serious risk of developing painful and difficult to heal ulcers.

The Frenchman Milian was the first to describe this clinical entity in 1929.[1] The first publications in English and French literature under the name atrophie blanche appeared in the early fifties.[2,3] Since then many articles have been published about AB, using different synonyms, such as capillaritis alba, atrophie blanche of Milian, livedo reticularis with summer ulceration's, livedo vasculitis, segmental hyalinizing vasculitis, vasculitis of atrophie blanche, PURPLE and livedo vasculopathy. This nomenclature can be very confusing [table 1] as some synonyms are used for different unrelated skin disorders.[4-15]

TABLE 1

Synonyms of atrophie blanche or white atrophy

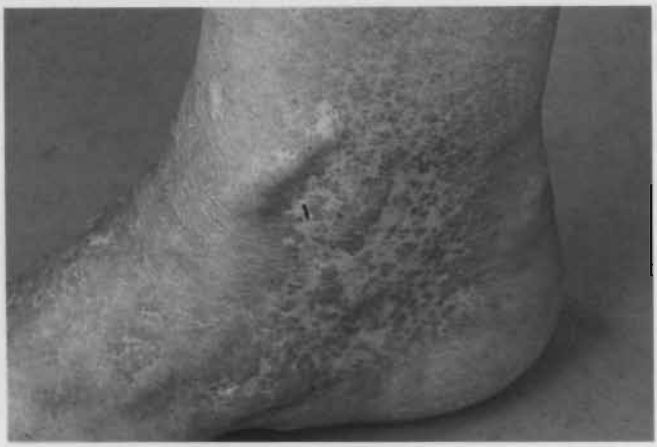
Nomenclature	Author	Year
Atrophie blanche	Milian[4]	1953
	Wilson[5]	1974
	Maessen-Visch[20]	1996
Capillaritis alba	Ellerbroek[4]	1953
	Metz[5]	1974
Atrophie Blanche of Milian	van der Molen[6]	1953
Livedo reticularis with summer ulceration's	Feldaker[7]	1955
Livedo vasculitis	Bard and Winkelmann[10]	1974
Segmental hyalinizing vasculitis	Bard and Winkelmann[8]	1967
	Pierard and Geerts[9]	1971
Vasculitis of Atrophie Blanche	Gilliam[11]	1974
	Schroeter[12]	1975
PURPLE (painful purpuric ulcers with reticular pattern of the lower extremities)	Milstone[13]	1983
(Livedo) Vasculopathy	Shornick[14]	1983
	McCalmont[15]	1992

Because there is a lot of controversy about AB, a review of the literature has been carried out on this entity and in order to summarise current knowledge regarding pathogenesis. Particular attention is given to the relation to other diseases and therapy.

CLINICAL PRESENTATION

The morphology of AB is very characteristic. Milian distinguished two forms of AB: "atrophie blanche en plaque" and "atrophie blanche segmentair".[1,16] He described "AB en plaque" as a smooth, depressed, ivory white plaque, of variable dimensions, from 0.5 to 15 centimetres, surrounded by a small pigmented ring of several millimetres in width, around which numerous teleangiectatic capillaries are arrayed [figure 1].[1]

FIGURE 1
Clinical aspects of a typical atrophie blanche lesion on the medial side of the ankle.



The morphology of "AB segmentaire" is less clear and has been clinically described by Milian as a scar-like lesion on one segment, a leg or a foot.
AB is described in 9%-38% of patients with chronic venous insufficiency (CVI).[6,17-20] The prevalence of AB in the general population is estimated to be between 1% and 5%. The prevalence of varicose veins varies between 15 and 50 %, of which 50 percent will develop CVI.[21-24] Especially in patients with recurrent venous leg ulcers the prevalence of AB is high, up to 73%.[18,20]
Ulcers of AB lesions can be extremely painful and shows a slow healing tendency. It is often underestimated that patients with AB and recurrent ulcers have considerable disability and that the costs of treating are enormous.[25]
Women are more often affected than men, M:F ratio is 1:4.[20,26] AB lesions can occur at any age, but the peak prevalence ranges from 30 to 60 years.[3,7,14,26] AB has also been described in children.[27,28] There are no data suggesting a geographic or racial difference.

Differential diagnosis of AB should include lichen sclerosis et atrophicans, scleroderma, malignant atrophic papulosis (morbus Degos), and scar formation.[29,30] Lichen sclerosis and scleroderma are mostly localised on the trunk, and the lesions are often not depressed. Histologically, a thickened dermis and a band of hyalinisation of the dermal collagen can distinguish these lesions. Malignant atrophic papulosis are mostly numerous small lesions distributed more proximal or on the trunk. Histology shows endovascular inflammation, proliferation and thickening of the deep dermal vessels. An atrophic scar is thin and wrinkled and shows no teleangiectatic capillaries.

In systemic diseases in which AB is described, the incidence of AB is unknown. Systemic diseases in which AB is seen include scleroderma and systemic lupus erythematodus (SLE).[10,31] The author suggest an incidence of less than 1% in systemic diseases is, based on literature and personal experiences. Recently a large group of patients with SLE was examined for skin disorders, cutaneous vasculitis was seen in 11% and livedo reticularis in 4%, however AB as special entity was not recorded or seen.[32]

In case reports AB is described in vasculitis necroticans, abdominal aortic pathology, cryoglobulinemia, thalassemia minor, essential thrombocytosis, glutathion reductase deficiency, Klinefelter's syndrome, Sneddon's syndrome, polycytheamia, gamma heavy chain disease, digital infarction, chronic myelogenous leukaemia and lymphoma .[31,33-44]

It is however generally accepted that AB is highly associated with CVI, as nearly all patients with AB show CVI.[6,21,45-48]

PATHOGENESIS

The underlying pathogenetic process of AB remains controversial. Successful fibrinolytic, antiplatelet and compression therapies of AB ulcers and the finding of occluded vessels in histology suggests a combination of coagulation and fibrinolytic disorders in relation to venous insufficiency.[31,49,50-52] It remains unclear what plays the most important role and whether coagulation and fibrinolytic disorders are caused by venous insufficiency or vice versa. Drugs that influence coagulation and fibrinolysis have been used since Gray *et al.* and Potter and Haberlin in the sixties suggested that local thrombo-occlusive processes were the cause for the ulcers that appeared in AB.[26,53]

There are several hypotheses postulated to explain the underlying mechanism of development of CVI, such as fibrin cuff, "white cell trapping" and microthrombi.

Fibrin cuff

Browse and co-workers suggested the "fibrin-cuff theory". They stated that as a result of CVI, a leakage of fibrinogen from the capillaries induces a fibrin-cuff around the capillaries leading to a barrier for oxygen and nutrients.[54,55] This would cause decreased transcutaneous oxygen values, as seen in CVI and especially in AB lesions.[56] Recently doubt has been expressed about this theory, as fibrin cannot be a serious barrier for oxygen; the fibrin cuffs are more an indication of a disturbed microcirculation, rather than an etiologic factor in CVI.[57-59]

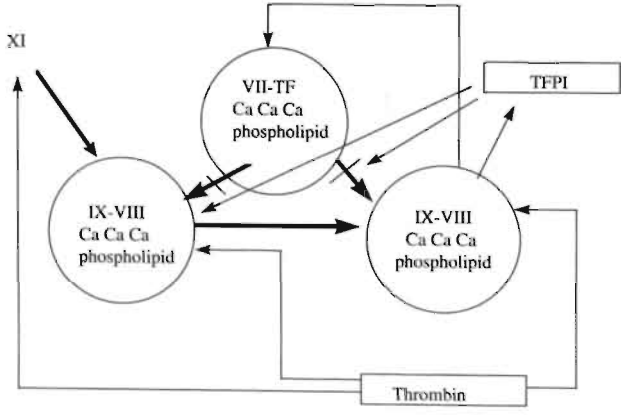
White cell trapping

Coleridge Smith *et al.* postulated the "white-cell trapping theory".[60] In this hypothesis white cells will, adhere ("trap") to the endothelium of the capillaries as result of venous hypertension, inducing the release of proteolytic enzymes and superoxyde metabolites causing destruction of the tissue.[60,61] This trapping seems to be a nonimmunological phenomenon, due to low flow in the wide capillaries, as no upregulation of binding molecules like ICAM, VCAM and ELAM is seen.[62]

Microthrombi

The microthrombosis theory of Bollinger is based on studies by capillary microscopy in patients with severe CVI and especially AB. Bollinger suggested that AB is a result of minor skin infarctions caused by microthrombi.[45,63]
Microthrombi may develop as result of disturbance in coagulation or fibrinolysis. Coagulation is characterised by the formation of fibrinogen into fibrin [figure 2].

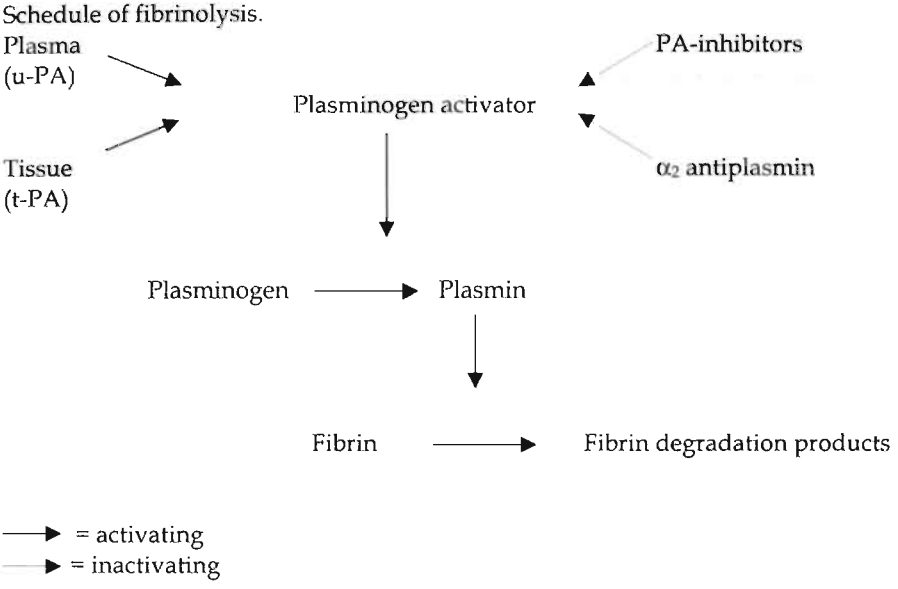
FIGURE 2
Schedule of coagulation cascade.



TF = tissue factor
TFPI = tissue factor plasminogen inhibitor
VII, VIII and IX = coagulation factor VII, VIII and IX

Fibrinolysis is performed by plasmin after activation by tissue plasminogen activator, urokinase or neutral proteases [figure 3].[64]
Under normal physiological conditions, procoagulant and anticoagulant mechanisms are delicately balanced. Disturbances may result in bleeding or thromboembolic disorders. Several procoagulation factors have been studied, suggesting a link between AB and disturbances in coagulation and fibrinolysis, but up till now no suggestive conclusions can be made.

FIGURE 3



Endothelium
A defect of endothelial cell plasminogen activator in patients with AB was suggested by Shornick *et al.*[14] Studies on the defective release of tissue plasminogen activator (t-PA) in patients with AB, however, did not prove a suppressed release of t-PA, since at least 20% of the 118 control persons showed the same values as patients with AB.[65,66] Also a high incidence of defective release of t-PA and increased levels of PA-inhibitor and a high incidence of antiphospholipid antibodies in patients with livedo vasculitis was reported by Klein.[67] Recently normal t-PA levels were found in patients with CVI and AB or dermatoliposclerosis.[68]
Increased levels of plasminogen activator inhibitor-1 antigen (PAI-1 antigen), fibrinogen and F VIII, von Willebrand Factor and a decrease in coagulation rate were found in a double blind study in 20 patients with venous ulcers compared with twenty healthy controls suggesting a relative thrombocytosis and hyperaggreability of platelets.[69] The time of blood sampling of individual patients

was not stated, however, which makes the results of PAI-1 less reliable since PAI-1 is subject to a diurnal fluctuation. Margolis *et al.* found significantly increased levels of PAI antigen in patients with CVI and dermatoliposclerosis, compared with healthy controls.[68] Increased levels of PAI antigen were also found in patients with CVI and AB, these were, however, not statistically significant. These data suggest that patients with AB have moderately abnormal fibrinolysis, but in a minor degree compared with patients with dermatoliposclerosis, who have substantial tendency to abnormal fibrinolysis.
Increased values of PAI were also found in patients with Klinefelter's syndrome and AB without venous insufficiency by Veraart *et al.*[40]

Platelets
Increased platelet aggregation was found in 7 patients with AB and livedo vasculitis, in which antiplatelet therapy was successful.[70] No control measurements were done, however, and further studies to investigate the relation between AB, CVI and abnormal platelet function were not performed.

Fibrin
An enhanced fibrin formation, as evidenced by elevated levels of total fibrin-related antigen and D-dimer was suggested by Falanga *et al.*[71] In 6 of 11 patients (55%) with venous disease with ulcers and in 3 out of seven patients (43%) with venous disease without ulcers the values of D-dimer were increased. Although these results are very suggestive of enhanced fibrin formation, the group studied is very small. No difference is made in patients with CVI with or without AB.
Elevated levels of fibrinopeptide A in 6 patients with livedo vasculitis were found by McCalmont *et al.*[15] Unfortunately no control group was studied.

Autoantibodies
The presence of AB in patients with systemic disease without CVI, also suggest a role of (local) coagulation disorders. For instance in patients with SLE, increased levels of antiphospholipid antibodies, such as lupus anticoagulants and anti-cardiolipines antibodies are seen.[72,73] The presence of antiphospholipid antibodies suggests a thrombotic risk, whereas lupus anticoagulants antibodies are associated with a higher thrombotic risk than anticardiolipines antibodies. The relation between major thrombosis, as in deep venous thrombosis, and microthrombi remains unclear. AB or livedo vasculitis has been described in two patients with anticardiolipin syndrome.[74] Recently, in a group of twelve patients with AB, anti-cardiolipines antibodies were detected in two patients, abnormal levels of circulating immune complexes were found in three patients, and two patients showed anti nuclear antibody (ANA) positivity.[75] The results were statistically not significant. In 4 of 6 patients with AB studied by Klein anticardiolipines antibodies were present, 2 of these patients showed a history of deep venous thrombosis.[67]
The percentage of overall thrombotic events in patients with SLE is 42% in antiphospholipid antibodies positive and 13% in antiphospholipid antibodies negative patients. The presence of antiphospholipid antibodies, however, may only represent a marker of a prothrombotic state, rather than a risk factor for the development of thrombosis.[76]

Essential cryoglobulinaemia was seen in 4 of 27 patients with AB, which was not related to CVI.[39]

Vasculitis

Some authors suggest a primary vasculitis as the underlying factor because of deposits of immunoreactants found in dermal blood vessel walls.[8,10,12] The role of immunologic factors in the development of AB is, however, unproved. Bard and Winkelmann believed that AB represented one phase of segmental hyalinizing vasculitis.[8] The importance of immunological factors in pathogenesis was stressed by Schroeter *et al.* who found positive immunofluorescence for complement factors and immunoglobulines in the superficial, mid-dermal and deep dermal vessels in a group of 15 patients with segmental hyalinizing vasculitis.[12] Reviewing the data of Schroeter and Winkelmann, however, there was no true vasculitis according to the international criteria of a leucocytoclastic vasculitis.[15,77] It is more likely that the immunological factors in the pathogenesis of AB are a secondary phenomenon.[14,78,79] This mechanism may be comparable with CVI, where a moderate to strong expression of ELAM-1 is seen under venous leg ulcers.[62]

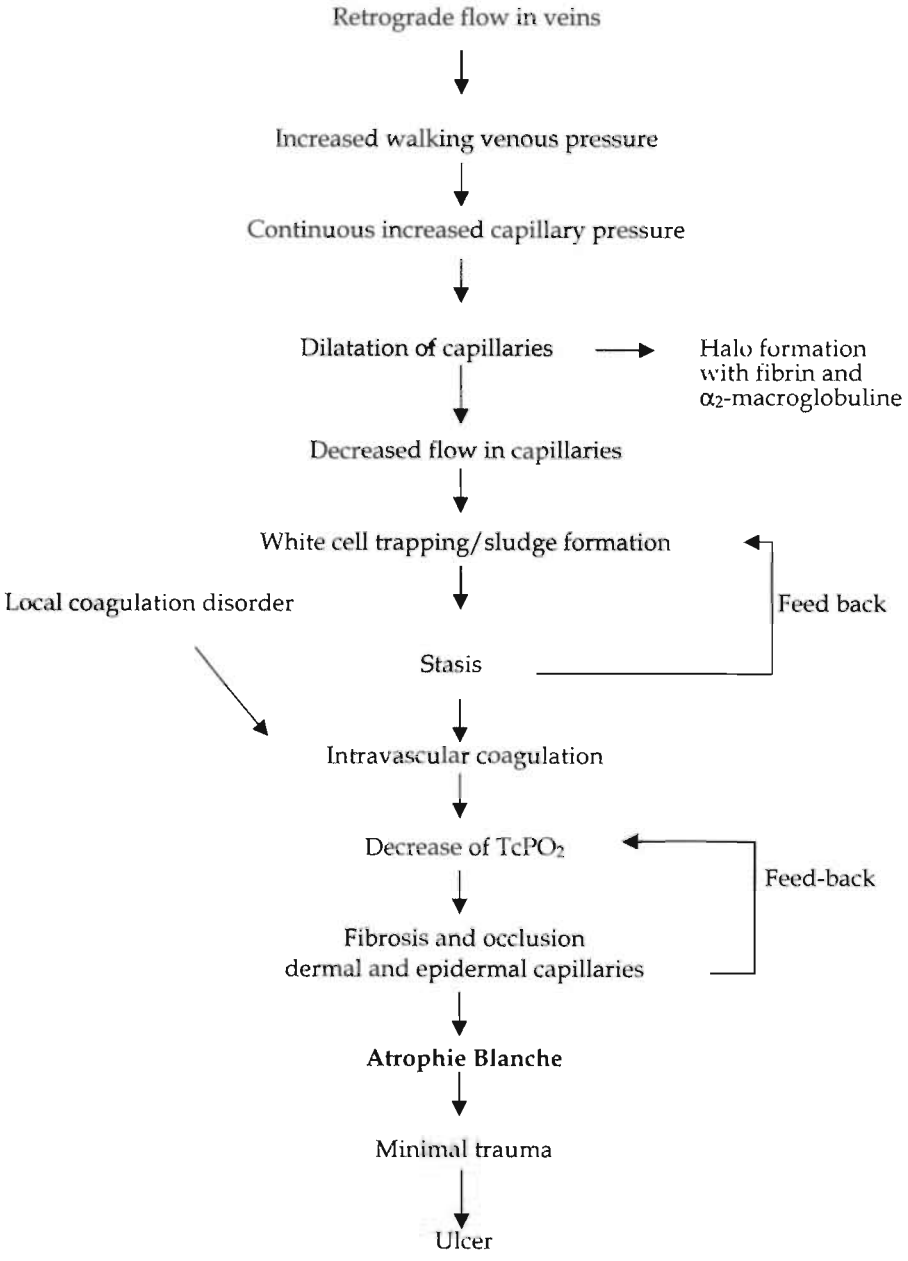
Infection

Milian and Gonin described AB in patients with syphilis, and tuberculosis, suggesting a chronic infection as cause for AB; however, this theory was never proved and seems now most unlikely.[14,80-82] The most likely explanation is that due to a high incidence of tuberculosis at that time, the incidence of AB seemed to be increased in patients with tuberculosis.

It is concluded that no studies can demonstrate increased fibrin formation, decreased fibrinolysis or vasculitis as cause for AB. Some studies are suggestive of thrombotic vasculopathy. Especially studies performed by Bollinger and coworkers with a capillary microscope strongly sustain the theory of microthrombi.[45,83,84] Thus, both CVI and systemic internal diseases might induce local coagulation disorders and impaired fibrinolysis, causing microthrombi, partly based on diminishing flow in the capillaries as result of CVI, partly by yet unknown mechanisms. It is suggested that in patients with CVI a decreased flow in capillaries may lead to increased sludge formation and cause increased coagulation which finally results in microthrombi [figure 4]. Further studies in this field are necessary.

FIGURE 4

Hypothesis of aetiology atrophie blanche.



HISTOPATHOLOGY

Data on histopathology are probably limited by the delayed healing that may follow biopsy. The choice of the biopsy site is important. Some findings are based on biopsies from the edge of ulcers, which differ from biopsies from fully developed AB lesions, causing many misconceptions in comparing unequal material.

Light microscopy

Light microscopy of a fully developed AB lesion is characterised by a thin and flattened epidermis with local parakeratosis and focal spongiosis and varying melanin deposition in the basal layer depending on the clinical hyper- or hypopigmentation.[5,26,77,79,85-88] The dermis is thickened and sclerotic with disappearance of the papillae.[79,85] This causes a scleroderma-like appearance.
The most pronounced abnormalities are found in the vessels of mainly the superficial dermis [figure 5]. The capillaries are dilated and show tortuous loops. Most vessels (capillaries and arterioles) show endothelial proliferation and are thickened and swollen .[5,39,79,85,89,90] Some vessels are occluded with fibrinoid material or erythrocytes.[14,26] Sometimes extravasation of erythrocytes with hemosiderin deposition is seen.[14,87] Occasionally entire vessels are replaced by fibrinoid material.[77]
Abnormalities of the vessels are seen both in the upper, middle and lower part of the dermis.[5,12,87] Perivascular a leucocytic or lymfohistiocytic infiltrate is seen of variable intensity, but never outspoken. The small number of polymorphonuclear leucocytes and the lack of nuclear fragments around the small vessels are the most important signs to differentiate between AB and leucocytoclastic vasculitis.

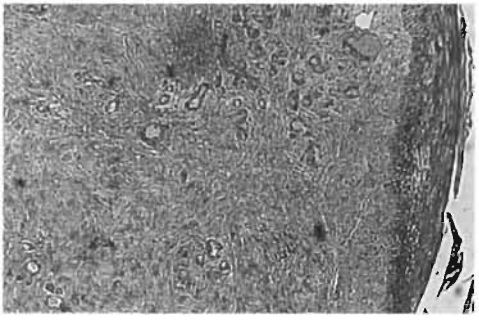
When ulceration occurs, histology is similar to venous ulcers, except that the epidermal necrosis is sharply defined, but bordered by hyperkeratosis and acanthosis.[18] In ulcerating AB lesions, a band of IgG, IgM and C3 can be seen around vessels.[12,14] These are the same vessel walls that show hyalinization in the hematoxylin-eosine sections. The immune deposits form a continuous outline of these thickened walls, with little or no deposition in the surrounding dermis. In early lesions only fibrin depositions are seen, without immunoglobulin or complement deposition. Some authors consider nonspecific staining as negative immuno-fluorescence since no typical granular immunofluorescence staining pattern is seen.[15] Antigen-antibody complexes are not the most important factor in the pathogenesis of AB, in contrast to leucocytoclastic vasculitis.[11,15,88]
Fibrin is deposited in linear layers around capillaries. Deeper in the dermis these fibrin cuffs disappear. Different markers for fibrin and fibrinogen have shown clear deposition of fibrin, but not of fibrinogen.[91]

Electron microscopy

Electron microscopy shows dilatation of capillaries (with a diameter up to 100 µm) with a thin endothelium, together with obliterated capillaries.[92] The vessels are

situated in a dense, fibrotic connective tissue. Fibrin deposition with occlusion of the lumina of superficial blood vessels has been described.[14,79] Erythrocytes and platelets are described trapped within the fibrin.[14] In older lesions endothelial cells are replaced by heavy fibrin depositions.[14,79]
The pericapillary space is oedematous and contains extravasated erythrocytes and macrophages.[87] Shornick *et al.* did not see any inflammatory cells near the vessel walls.[14] Leu *et al.* noticed occasional lymphocytes and plasmocytes, but no granulocytes.[87] Zabel and Hettewer, however, described an infiltrate in which both granulocytes, lymphocytes, plasmocytes, granulocytes and macrophages are seen.[79]
It can be concluded that the most important histological abnormality are the dilated capillaries which show tortuous loops and are partly occluded by fibrinoid. Immunofluorescence staining can be considered as a non-specific finding.

FIGURE 5
Histology of atrophie blanche (100x); a flattened epidermis and tortuous capillaries which are partly occluded.



MICROCIRCULATION

Microcirculation can be studied with capillary microscopy, transcutaneous oxygen measurements ($TcPO_2$), laser Doppler flowmetry (LDF) laser Doppler perfusion imaging (LDPI) and microlymphography.

Capillary microscopy and $TcPO_2$

Investigations by capillary microscopy give a good impression of the morphology of the capillaries. In healthy skin capillary microscopy shows a regular pattern of small capillaries.[93] In AB lesions an (almost) avascular field with no recognisable capillaries is seen in the center.[45,83] A capillary density of zero to less than 10/mm^2 is measured in these areas.[83,94] At the edge enlarged capillaries are visible lying approximately parallel to the skin surface, very characteristic of AB. The more remote capillaries show a less altered morphology. This pattern is compatible with that of CVI disturbances without AB.[45]
With intravenous bolus injection of Na-fluorescein a more functional aspect of microcirculation is obtained.[84,94,95] In the border of AB lesions the dye arrives in

the same time as in healthy controls (ca 30 s). The dye reaches the centre of the avascular lesion of AB only after 40 minutes.[84]
Transcutaneous oxygen measurements show $TcPO_2$ values close to 0 mmHg. In border zones of AB the mean $TcPO_2$ reaches 24.0 mmHg, compared with 56.8 mmHg in control subjects.[83] $TcPO_2$ values in patients with CVI without AB differ significantly from healthy persons, dependent on stage of CVI.

Laser Doppler flowmetry and laser Doppler perfusion imager
Laser Doppler flowmetry (LDF) and laser Doppler perfusion imager (LDPI) measure the flux in nutritive and thermoregulatory capillaries of the dermis. Measurements show an increased median basic resting flux in patients with CVI and AB lesions compared with normal skin.[96-99] Venous hypertension, induced by a upper thigh cuff, results in a similar decrease of flux in AB lesions or normal skin (46% in normal, 56% in AB lesions).[99]

Lymphography
Microlymphography is performed with FITC-dextran, which is injected subepidermally. In normal skin a regular, intact network of hexagonally shaped meshes is seen.[100,101] In patients with severe stages of CVI, the lymphatic capillary network at the medial ankle is fragmented and destroyed, and the permeability of the remaining microlymphatics is increased.[59,100-102] In some patients dermal backflow (cutaneous reflux) is described.[102] In patients with AB an abnormal lymphatic flow was seen by Partsch.[103]

Technetium scanning
In differentiating AB from Kaposi's sarcoma and pseudo-Kaposisarcoma, radionuclide scanning can be used. ^{99m}Tc scanning is positive in cases of (pseudo)-Kaposi sarcoma and negative in patients with AB.[104]

THERAPY

As AB was initially described as a consequence of syphilis, Milian advised antisyphilitic therapy. After this theory had been abandoned, many other therapies were used. There are as many theories described as there are practitioners treating AB.[105] Different surgical therapies have been used in the past such as galvanocautery, sympathectomy, excision *in toto* and paratibial fasciotomy, with no or only temporary relief.[3,26,105-108] The use of X-ray is described, which is now obsolete.[2,8] Systemic corticosteroids and topical steroids as well as intralesional injections of lidocain and triamcinolone give poor results.[26,46,109,110] Treatment with acyclovir is described in a case report.[111] All above-mentioned therapies are, however, almost all case-reports, and their therapeutic effect is doubtful. Good clinical trials (prospective, randomised, placebo controlled) which fulfil the Cochrane criteria are not found in literature.[112]
As CVI is seen in about 99% of the patients with AB, therapy should be focused on this aspect. Before therapy is started the presence of CVI must be determined.

TABLE 2
Different therapies used in AB lesions

Medicine	Dose	N	Success rate	Length of therapy	Mechanism	Author	Com ments
Phenformin Ethylestrenol	50 mg 1xdd 2 mg 2xdd	5	100%	4 months	Fibrinolysis and increased tPA activity	Gilliam[11]	1,2
Phenformin Ethylestrenol	not stated	10	100%	4-8 weeks	Fibrinolysis and increased tPA activity	Shornick[14]	1,2
tPA	10 mg	2	100%	2 weeks	Fibrinolysis	Klein[62]	1,2
tPA Aspirin Warfarine	10 mg, 81mg 2 to 4 mg	4	100%	2 weeks	Fibrinolysis	Klein[62]	3
Aspirin Dipyridamolee Ticlopidine	82 mg 1xdd 225 mg 1xdd 200 mg 1xdd	2		45 days	Anti-platelet aggregating	Yamoto[119]	3
Aspirin Dipyridamolee	325 mg 3xdd 75 mg 4x dd	7	86%	2-11 months	Anti-platelet aggregating	Drucker [64]	1,2
Aspirin Dipyridamole	325 mg 2xdd 50 mg 3xdd	2	100%	4 weeks	Anti-platelet aggregating	Kern[120]	3
Aspirin Dipyridamole	365 mg 1xdd 75 mg 1xdd	8	100%	not stated	Anti-platelet aggregating	Elisaf[121]	1,2
Phenidine		1	100%?	3 years	Anticoagulant	Champio n[122]	3
Aspirin Dipyridamole	150 mg 1xdd 50 mg 3xdd	27	48%	8 weeks	Not in discussion	Yang[39]	1,2
Heparin sodium	5000 IE 2xdd	15	70%	8 weeks	Not in discussion	Yang[39]	1,2
Heparin sodium	5000 IE 2xdd	1	100%	3 months	Anticoagulant	Jetton[49]	3
Heparin sodium	5000 IE 2xdd	1	100%	1 week	Anticoagulant	Heine [50]	2,3
Heparin sodium LMWH (Nadro-parin calcium)	12300 IE 2xdd	4	improve d	20 days	Anticoagulant, fibrinolysis	Gunier[123]	1,2
Prostaglandin E_1	10 ng/kg 2hrs/day	1	100%	20 days	vasodilatation, anti-platelet aggregating	Uchida[124]	2,3
Lipoprosta-glandin E_1	10 µg	1	100%	14 days	vasodilatation, anti-platelet aggregating	Nonaka[125]	2,3
Nifedipine	10-20 mg 3xdd	1	100%	3 months	vasodilatory effect	Purcell[126]	2,3
Sulfasalazine	1 gr 3xdd	2	100%	3 months	unclear	Gupta[127]	2,3
Sulfasalazine	500 mg 3xdd	8	87.5%	8 weeks	Inflammatory immunologic, platelets	Bisalbutra [128]	1,2
Pentoxifylline	400 mg 3xdd	6	improve d	9 weeks + MT	Bloodviscosity	Sauer[129]	1,2
Pentoxifylline	400 mg 3xdd	8	80%	3-11 months	Bloodviscosity erythrocyte flexibility	Sams[130]	1,2,4
Pentoxifylline Aspirin Dipyridamole	400 mg 3xdd 300 mg 1xdd 500 mg 3xdd	3	67%	2-7 months	Bloodviscosity erythrocyte flexibility	Sams[130]	1,2,4

N= number of patients
LMWH= Low molecular weight heparins
MT= maintenance therapy

1= not placebo controlled
2= based on clinical improvement
3= case-report
4= new ulcers during therapy

The use of adequate compression therapy is essential and is still the cornerstone in the treatment of venous disease.[5,6,51,113-115] To maintain a situation of oedema reduction, medical compression stockings should be prescribed.[115] AB is clinically found to be partially reversible after treatment with well adapted elastic support - (compression).[116] In cases of superficial venous insufficiency, treatment of the veins can be considered, for example by means of sclerocompression therapy of veins proximal and distal of AB lesion, as described by Tazelaar.[19,117,118]
As impaired haemostasis and fibrinolysis may play an important role in aetiology, therapy should modulate or interfere with microcirculatory disturbances [table 2].

Three major groups of drugs are used in the treatment of AB:

Drugs stimulating endogenous fibrinolytic activity
The combination of phenformin and ethylestrenol enhances endogenous blood fibrinolytic activity by increasing plasminogen activating enzymes.[131] Gilliam *et al.* have reported good clinical results with these two drugs in treating AB ulcers.[11] In 1977 phenformin was removed from the general market by FDA decision because of its side-effects. Since ethylestrenol alone is not effective, other drugs are suggested to use as a substitute for phenformin and ethylestrenol, such as low dose tissue plasminogen activator (t-PA).[67] Most results described are case reports. Klein treated 2 patients with t-PA, during two weeks and 4 patients with t-PA and aspirin and warfarin.[67] In some patients $TcPO_2$ improved during treatment and all patients improved clinically. t-PA is introduced commercially as a specific fibrinolytic factor, lysing thrombi so its therapeutical effect on AB can be studied.

Drugs inhibiting thrombus formation (antiplatelet and anticoagulant)
Aspirin and dipyridamole are used by different authors, with both good and poor clinical and subjective improvements.[39,49,70,119-121] Aspirin is a cyclooxygenase inhibitor that suppresses thromboxane A_2 and prostaglandin I_2.[132] A good double-blind, randomised study, placebo controlled, with aspirin was made by Ibbotson *et al.* in patients with venous ulcers in which an increased rate of ulcer healing was seen in the aspirin-treated group.[69] dipyridamole inhibits synthesis of thromboxane A_2, and stimulates release of prostaglandin I_2.[133] Intravenous administration of prostaglandin E_1 has been described because it has vasodilator, platelet aggregation inhibiting and erythrocyte deforming properties.[124,125] Pentoxyfylline has been used because of its improving effect on erythrocytes deformability and lowering effect on blood viscosity.[129,130] Both aspirin and pentoxyfylline have, besides the above mentioned properties, a positive effect on rheology and prevent sludge formation. Anticoagulants have been first suggested in 1962.[122] Jetton and Heine used minidoses of heparin.[49,50] Heparin does not only inactivate the coagulation cascade, it also decreases blood viscosity and increases fibrinolytic activity.[50,134,135] Promising results with low molecular heparins were described by Gunier, who reported rapid pain relief and cessation of the necrotic process and tissue regeneration in 4 patients.[123]

Vasodilatating drugs
Purcell report the use of nifedipine.[123] Recently, Gupta has reported good clinical effect with sulfasalazine, which is confirmed in 8 other patients.[127,128] The mechanism of sulfasalazine is unclear. It might have an antiinflammatory and a thromboxane inhibiting effect.

Best choice of drug
The first choice of treatment for AB ulcers in patients with CVI remains, however, compression therapy. Reviewing above-mentioned studies, the most promising effects in slow healing ulcers might be expected from heparin, aspirin and dipyridamole.

CONCLUSION

Atrophie blanche cans clinically be divided into a segmented and a plaque form, as performed by Milian did in 1929.[1] In daily practice this classification is not useful, since both forms are seen in association with different diseases. It is however important to make a difference whether AB belongs to the complex of symptoms of CVI, which is mostly the case, or whether AB is the result of systemic diseases. A clinical and technical workup for venous diseases should always be performed.[136] Certain aspects should be considered, reviewing the different morphologic descriptions of AB. When AB is described with systemic disorders, atrophy is seen, but hyperpigmentation and teleangiectatic capillaries are not described, and are not found in histopathology. It is not always clear whether these disorders only resemble AB, and are in fact only scars.[137-139] Originally Milian described that AB could be mistaken for a scar, but probably a scar also can be mistaken for AB. Especially AB segmentaire cannot clearly differentiated from other atrophies. So, only when a combination of one or several white, smooth, depressed, ivory white plaques of variable dimensions, surrounded by a small pigmented ring in and around which numerous teleangiectatic capillaries are arrayed, can the diagnosis AB be made.
In almost all cases of histology of AB obstruction of small vessels is described, sometimes these are found predominantly in the upper dermis, sometimes predominantly in the lower dermis. The term livedo vasculitis and other synonyms should be avoided. In the future it is advised to use the term atrophie blanche instead of livedo vasculitis.
The presence of avascular fields in AB lesions may be caused by a combination of microthrombosis causing microinfarctions, impaired haemostasis and fibrinolysis and endothelial damage. Trapping of leucocytes may also cause microvascular occlusion, reducing the number of functional capillaries.
AB can develop after ulceration or can be a *de novo* phenomenon. It is hypothesised that local dysregulation of coagulation and impaired fibrinolysis are most important in the pathogenesis. Inflammation is only a secondary phenomenon. Different disorders such as CVI and several systemic diseases might function as a trigger for this dysregulation.
In patients with AB, especially in the area between the knee and the ankle (gaiter area), a phlebological analysis is indicated to diagnose or exclude CVI. If CVI is

excluded, or the lesions are located elsewhere than in the medial ankle region area, further investigations for internal diseases are indicated. In some cases, when further investigations show no abnormalities, AB can be seen as a idiopathic disease.

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CHAPTER 3

PREVALENCE OF ATROPHIE BLANCHE IN PATIENTS WITH A VENOUS LEG ULCER (RÉPERCUSSIONS DE L'ATROPHIE BLANCHE SUR LES PATIENTS ATTEINTS D'UN ULCUS CRURIS VENOSUM)

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SUMMARY

Atrophie blanche is a characteristic cutaneous disorder, which can be considered as belonging to the complete syndrome of chronic venous insufficiency. The prevalence is not clear. We studied a group of 126 patients (151 legs), presenting with a leg ulcer in an outpatient clinic in the south of the Netherlands. In 31% of the male patients and 44% of the female patients atrophie blanche was part of the clinical symptomatology of chronic venous insufficiency. This is a higher prevalence than reported in the literature. Patients with atrophie blanche showed significantly more recurrent ulcers than patients without atrophie blanche. Aetiology of atrophie blanche is still unclear. One of the most important theories is that a disturbed microcirculation as result of chronic venous insufficiency leads to microthrombi and local occlusions of the vessels. Patients with atrophie blanche are seen more often in out patient clinics specialised in phlebology. Ulcers of atrophie blanche form a select group of ulcers in patients with chronic venous insufficiency with a high risk for recurrences.

RÉSUMÉ

L'atrophie blanche (AB) est une anomalie caractéristique de la peau est considérée surtout en Europe, comme faisant partie intégrante du syndrome de l'insuffisance veineuse chronique (IVC). Ses répercussions restent obscures.
Nous avons étudié un groupe de 126 patients (151 jambes) qui se sont présentés atteints d'ulcus cruris dans un service de dermatologie du Sud des Pays-Bas.
Chez 31% des hommes et 44% des femmes, l'AB ne représente qu'une partie de la symptomatologie de l'IVC mais en réalité ces répercussions sont plus importantes qu'on ne le décrit dans la littérature. Dans le groupe de patients atteints d'AB, il était très souvent question d'une récidive d'ulcus cruris. L'éthiologie de l'AB est encore incertaine. L'une des théories les plus reconnues admet que l'IVC provoque une pertubation de la microcirculation, des microthromboses sources d'occlusions veineuses locales. Compte tenu de la gravité des répercurssions, les patients atteints d'une AB ulcérée sont hospitalisés dans un service specialisé en phlébologie. Les AB ulcérées constituent un groupe d'ulcères propice aux récidives.

INTRODUCTION

Atrophie blanche (AB) belongs to the complex of symptoms of chronic venous insufficiency (CVI) and is often seen in patients with recurrent leg ulcers. Leg ulcers in patients with atrophie blanche are characterised by severe pain and slow wound healing.
Besides CVI, atrophie blanche is seen in patients with lupus erythematodus, scleroderma, cryoglobulinaemia, thallassemia and Klinefelter's syndrome [table 1].[2-6]
The frenchmen Milian was the first to introduce the term atrophie blanche for smooth, depressed, ivory white disorders with dilated capillaries, which are mainly located on the distal part of the leg.[7] His original hypothesis that atrophie blanche was caused by *"Treponema Pallidum"* was never proved. Since that time, several hypothesis about the aetiology of atrophie blanche have been raised. The most accepted theory is that atrophie blanche is part of CVI.[8,9] As a result of microthrombi, occlusion of capillaries is seen, leading to local dermal disorders, such as atrophie blanche.

TABLE 1
Atrophie blanche is associated with several disorders.

Disorder	Author
Thalassemia minor	Berge (3)
Cryoglobulinemia	Ryan (4)
Systemic lupus erythematodus	Ryan (4) Bard (5) Stevanovic (6)
Scleroderma	Ryan (4) Bard (5) Stevanovic (6)
Klinefelter's syndrome	Veraart (7)

Atrophie blanche is defined as smooth, depressed, ivory white plaque of variable dimensions, surrounded by a small pigmented ring of several millimetres in width, around which numerous teleangiectatic capillaries are arrayed. Atrophie blanche is mainly located on the medial or lateral malleolus. Besides the malleolus, atrophie blanche is seen on the dorsal side of the foot and pretiabial. Atrophie blanche is seldom seen on other parts of the body. If atrophie blanche is located on other parts than the leg, it is mostly associated with internal diseases. Milian originally distinquished two forms of atrophie blanche: "atrophie blanche en plaque" and "atrophie blanche segmentaire". The last is hard to differentiate from a scar.

According to the classification from Widmer, atrophie blanche belongs to stage two of CVI.[10] In a study of Van der Molen in 1953, only 9% of the patients with a leg ulcer suffered from atrophie blanche.[11] This is a small percentage, considering that atrophie blanche forms a symptom of CVI. Prevalence between 11% and 37% is found in several studies by both dermatologists and surgeons.[12-15] Because it is still unclear how often atrophie blanche is seen in patients with recurrent leg ulcers, and since recurrent leg ulcers forms a large socio-economic problem, we studied the prevalence of atrophie blanche in patients with (recurrent) leg ulcers .

METHODS

All patients visiting the phlebological outpatient clinic of the Sint Joseph hospital for a venous leg ulcer in the period between 1-1-1990 and 30-6-1994 were included. Patients were asked whether they suffered from diabetes mellitus, arterial diseases and autoimmune diseases. Phlebological examination was done clinically: the presence of corona phlebectatica, dermatoliposclerosis and atrophie blanche was noted. Additional investigations to measure ankle/arm index and venous reflux (with digital photoplethysmography) were done if necessary.

RESULTS

In this period 126 patients were seen, of which 25 had a leg ulcer on both legs. Totally 151 legs were seen with a leg ulcer, 82 with an ulcer on the left leg and 69 on the right leg. Thirty five men were seen and 91 women with an average age of 68.2 years (24-93). The average age of the women was, 70.0 years, which was significant older than the average age of the men (63.4 years, p=0.02).
Atrophie blanche was seen in 31% of the men and in 44% of the women, this difference was, however, not statistically significant [table 2].
During this period, 30 of the 126 patients (24%) developed recurrent leg ulcers. In total recurrent leg ulcers were seen in 52 legs (34%), 34 times at the left leg and 18 times at the right leg. Recurrent leg ulcers were more often seen in atrophie blanche lesions, 37 times (71%), this difference is statistically significant (p=0.0004).

TABLE 2

126 patients with leg ulcers.

	Men	Women	P value
Number of patients	35	91	
Mean age	63.4 years	70.0 years	$p = 0.02$
Number of leg ulcers	40	111	
Ulcer located left/right leg	23 / 17	59 / 52	NS
Recurrent leg ulcer without AB	4 (11%)	11 (12%)	NS
Recurrent leg ulcer with AB	8 (23%)	29 (32%)	NS
Number of patients with AB	11 (31%)	40 (44%)	NS
Average age of patients with AB	55.3 years	67.6 years	$p = 0.04$
AB left leg	10	22	
right leg	1	13	
both legs	0	5	

AB: Atrophie blanche
NS = not significant

In the last two years, 25 patients were seen with atrophie blanche, 15 with atrophie blanche on one leg and 10 with atrophie blanche on both legs. This group of patients consisted out of 6 men and 19 women [table 3]. Atrophie blanche was seen in 9 patients on 1 location, in 9 patients on 2 locations, in 2 patients on 3 locations, in 4 patients on 4 locations and in 1 patient on 5 locations. In this group of patients, 25 suffered from mild hypertension, 2 patients suffered from diabetes mellitus and 2 patients suffered from arterial insufficiency. Non of the patients had autoimmune disorders or cryoglubinemia.
Only one patients noticed an increase of complaints during the summer and a decrease during the winter. Other disorders consisted of arthrosis of the hip (1 time), cardiovascular accident (1 time) and decompensatio cordis (1 time).

TABLE 3
Location of atrophie blanche in 25 patients.

Location	Number of patients
Left medial malleolus	23 (92%)
Left lateral malleolus	11 (44%)
Pretibial left	2 (8%)
Right medial malleolus	10 (40%)
Right lateral malleolus	6 (24%)
Right leg: pretibial	1 (4%)
dorsal side of feet	1 (4%)

DISCUSSION

Our results only partly confirm the results of Metz, who described that atrophie blanche was mainly seen in middle aged women.[16] Men with atrophie blanche were seen in 31% in our group of patients with atrophie blanche, while Metz only described 5-10%. No patient under the age of 27 was seen.
The prevalence of atrophie blanche in patients with an active leg ulcer in this study is very high (40%) and has not been described before. Only two times atrophie blanche is described in around 30% of patients with CVI.[14,15] This high prevalence may be explained by the slow healing tendency of leg ulcers in atrophie blanche. In the Netherlands most patients with a venous leg ulcer are treated by a family doctor. Only when he does not succeed, patients are sent to an outpatient clinic. As a result the group of patients seen in an outpatient clinic are a selected group of patients, these are more often patients with slow healing leg ulcers.
The pathogenesis of atrophie blanche is still unclear. The hypothesis of Milian that atrophie blanche is the result of "*Treponema Pallidum*" has been abonded.[7] In the fifties it was already suggested that atrophie blanche is the result of CVI and varicosis.[11,17] Other authors suggest that atrophie blanche is the result of vasculitis.[2,18-20] Stevanovic hypothesised that atrophie blanche is the result of occlusion of small vessels in the skin.[5] Shornick divided atrophie blanche into a primary and secondary form.[21] Primary atrophie blanche is the result of a vasculopathy, which is associated with a decrease of plasminogen activator, while the secondary form is related to autoimmune diseases.[8,9] At this moment the most accepted theory is

that atrophie blanche is the result of CVI. As a result of a diminished capillary flow, microthrombi develop, which results in small infarct of the skin.[8] Obliteration of some of these small vessels result in a vascular areas, such as atrophie blanche.

Histopathology of atrophie blanche is characterised by tortuous capillaries, which sometimes are replaced by fibrinoid material. The decreased number of capillaries was confirmed by capillary microscopy by Bollinger *et al.*[8,22] They found avascular areas in atrophie blanche.[22]

It is unclear why not all patients with CVI develop AB. We hypothesise that as a result of retrograde flow, the venous pressure and capillary pressure increases, resulting in venectasia with a decreased flow [figure 1]. Sludge formation, white cell trapping and fibrinolytic disorders will finally result in AB. It is most likely that in the fibrinolytic disorders especially local processes are involved.[23] Increased levels of plasminogen activator inhibitor support this theory.[6] Also the increased concentration of fibrinopeptide A, a symptom of increased thombogenic state, is suggestive for a role coagulation disorders in AB.[24]

Several therapies for the treatment of venous leg ulcers with and without AB are described. Besides compression therapy, case report with the use of heparins, dipyridamole, aspirin and salazopyrine are described, with varying results.[25-27]

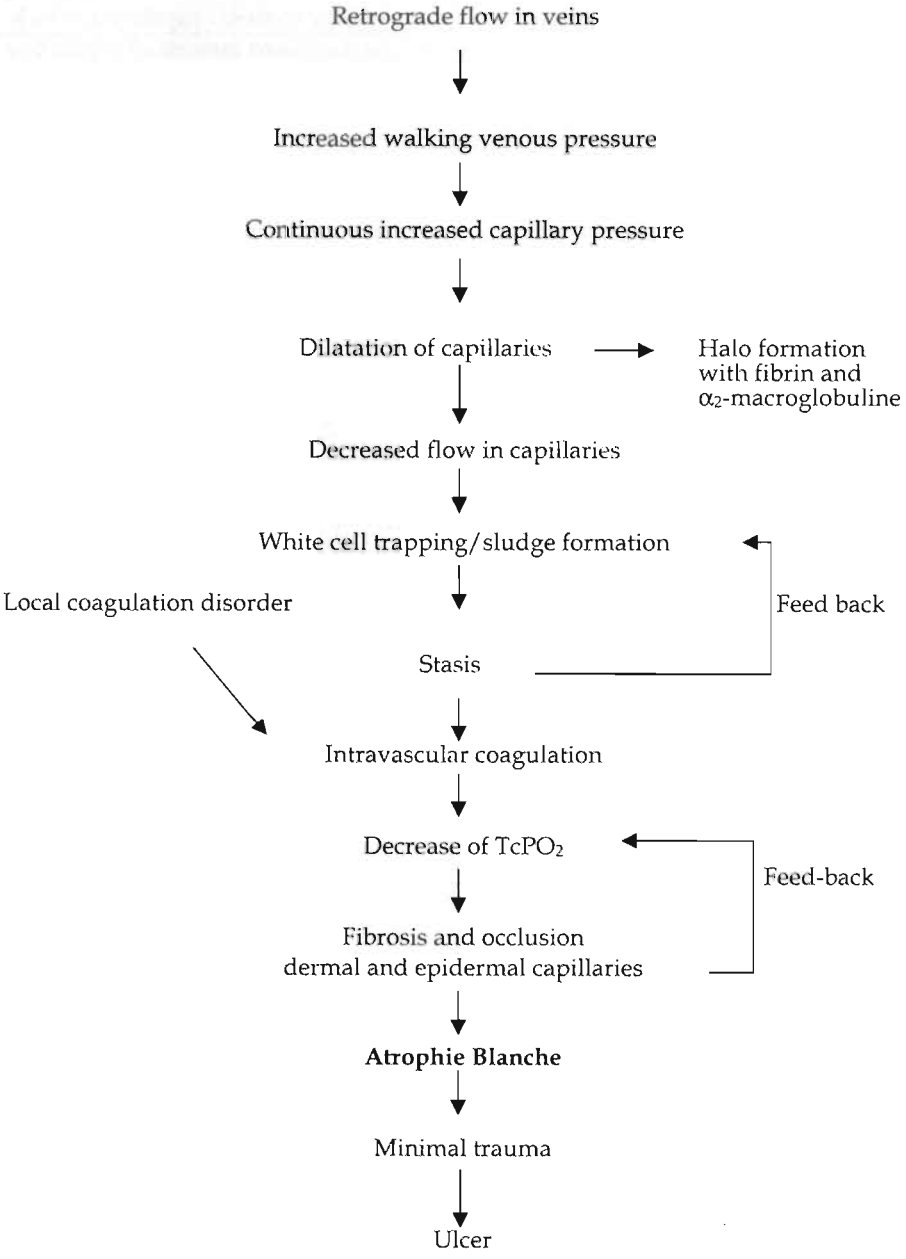
The recurrence of leg ulcers in the group of patients in this study can be explained by non-compliance behaviour of the patients. Especially continuous compression therapy is for a lot of patients very difficult. Another reason might be the presence of coagulation disorder in patients with AB.

It is very likely that in patients with AB, besides increased venous pressure, local fibrinolytic disorders play an important role in pathogenesis. Treatment with compression therapy and anticoagulant therapy or fibrinolytic therapy would be necessary to prevent recurrent ulcers. Further studies are necessary to assess the decrease of the recurrence rate in patients with AB.

It is concluded that in patients with long lasting CVI, decompensation of CVI occurs, resulting in recurrent leg ulcers and an increase in prevalence of AB. Since ulcers in AB show a slow tendency of healing, adequate compression therapy in an early stage seems important to prevent the recurrence of leg ulcers in this area.

FIGURE 1

Hypothesis of aetiology atrophie blanche.



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CHAPTER 4

CHANGES IN MICROCIRCULATION IN PATIENTS WITH ATROPHIE BLANCHE VISUALIZED BY LASER DOPPLER PERFUSION IMAGING AND TRANSCUTANEOUS OXYGEN MEASUREMENTS

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ABSTRACT

Objective
To quantify differences in microcirculation in atrophie blanche (AB) in patients with chronic venous insufficiency (CVI) and in healthy controls before and after venous occlusion.

Design
Prospective study in a single patient group.

Setting
Department of Dermatology, University Hospital Maastricht, the Netherlands.

Patients and methods
16 patients with CVI and large lesions of AB, 10 patients with CVI without AB and 10 healthy controls were enrolled in the study. Laser Doppler Perfusion Imaging (LDPI) measurements were performed in and outside large lesions of AB and in healthy controls. Transcutaneous oxygen ($TcPO_2$) measurements were performed in patients with CVI with and without AB and in healthy controls.

Results
Median basic resting flow was higher in AB than in healthy controls (0.67 mV versus 0.21 mV, p=0.002). The venoarteriolar response(VAR) was increased significantly in AB (58% versus 43%, p=0.04). A significant decrease in $TcPO_2$ values occurred in AB lesions with 40 mmHg, in CVI skin with 60 mmHg and in healthy controls with 80 mmHg artificially induced venous pressure.

Conclusion
Basic resting flux in AB measured with LDPI is increased compared with clinically normal skin. The decrease in flux on venous occlusion is larger in AB than in healthy controls.

Key words: white atrophy, laser doppler perfusion imager, venoarteriolar response

INTRODUCTION

Atrophie Blanche (AB) is a clinical disorder often seen by dermatologists and phlebologists. AB is described in scleroderma, systemic lupus erythematodus and cryoglobulinaemia.[1-3] Most AB lesions seen in patients, however, are a result of chronic venous insufficiency (CVI).[4-8] In 10 - 30% of patients with CVI, AB is seen.[8-10]

CVI is a complex of symptoms caused by venous reflux, due to valvular incompetence of deep, superficial and/or perforating veins, and leading to an increased walking venous pressure. The increased venous pressure of the macrocirculation is transmitted retrogradely into the microcirculation of the skin, resulting in changed morphology of the capillaries. All well-known skin changes in CVI are the result of the disturbed macro- and microcirculation.

In patients with AB, not only the morphology of capillaries is changed, but also the number of capillaries is reduced and the capillaries are often obstructed.[11]

Changes in microcirculation can be studied with transcutaneous oxygen measurements ($TcPO_2$)[12], capillary microscopy[13], laser doppler flowmetry (LDF)[13] and laser doppler perfusion imaging (LDPI).[14] In the area of AB, values of $TcPO_2$ are reduced, even to zero.[12] Capillary microscopy in CVI, and especially in AB shows dilated and elongated vessels with a winding, glomerulus-like appearance and an increase in the pericapillary leakage diameter (halo).[13] LDF shows increased flux in the skin of patients with CVI.[13,15-18] Both a decreased vasoconstrictor response on standing in patients with severe CVI[15,16], as well as an unchanged vasoconstrictor reaction in medium to severe CVI have been described.[13,18] No specific LDF measurements in AB are reported.

LDF, however, is limited in its clinical usefulness by its poor reproducibility.[14] The main disadvantages are its spatial resolution (1 mm^2), artefacts of movement and the difficulty in applying the probe exactly and directly to the previously measured tissue.[14]

Recently LDPI has been developed to avoid the disadvantages of LDF and is described as highly reproducible.[14,19,20] LDPI measures perfusion of the skin in a much larger area and yields an average value of 4096 points. There is no contact between the scanner and the skin, so measurements do not influence the blood flow. LDPI therefore has many advantages above LDF for assessment of microvascular perfusion of the skin.[20]

The aim of this study was to determine alterations in flux and transcutaneous oxygen values in AB lesions and healthy looking skin in patients with CVI before, during and after venous occlusion. Decreased numbers of capillaries and arterioles in AB lesions suggest an increased flux in AB lesions at rest and an altered venoarteriolar response might be found. Our aim was to evaluate the flux in the capillaries in AB.

PATIENTS AND METHODS

Patients

Group A: Sixteen patients (8 males, 8 females, average age 61 (32-80) years), with CVI and AB plaque lesions at the medial ankle, larger than 2 x 2 cm.
Group B: 10 patients (5 male, 5 female, average age 65 (43-75) years) with CVI without AB and dermatoliposclerosis.
Group C: ten healthy controls (5 males, 5 females, average age 53 (32-74) years).
CVI was defined as reflux in the superficial, deep and or perforating veins with doppler/duplex ultrasound, decreased venous refilling time (<15 s) as measured by light reflex rheography and by clinical symptoms of corona phlebectatica, AB and dermatoliposclerosis. Exclusion criteria were arterial insufficiency, diabetes and coagulation disorders. All CVI patients were well compensated and had been wearing elastic compression stockings for at least the last six months. Three patients were known with mild, well-controlled hypertension.
LDPI measurements were performed in AB lesions in group A, control measurements were performed in the medial ankle region in group C and in the knee region of group A.
$TcPO_2$ measurements were performed in 9 AB lesions of group A and in adjacent non-AB skin. Control measurements were performed at the medial ankle of patients in group B and C.
The Ethics Committee of the University Hospital of Maastricht approved the study.

Laser Doppler perfusion imager

In order to measure skin perfusion all measurements were performed with the PIM.Lisca version 2.4 (Linkoping, Sweden). A full description of the Laser-Doppler together with an evaluation of the laser-technique is given elsewhere.[14] In brief the instrument generates a colour-coded image of the spatial distribution of tissue perfusion [figure 1]. The LDPI comprises a 2-mW helium-neon laser whose beam is directed at the tissue via an optical scanner. This consists of two mirrors controlled by two stepping motors, which sequentially measure up to 4096 points. The back-scattered light is detected by a photo diode at a distance of about 15 to 20 cm from the tissue surface. An area of 40 cm^2 can be scanned. Each colour-coded pixel represents approximately 1 mm^2 of tissue. The scanner is controlled by a personal computer, which is also used for image display and storage. The images are displayed with colours representing a scale of mean blood velocity.[15]

Transcutaneous oxygen measurements

$TcPO_2$ measurements were performed with the transcutaneous TCM 2 (Radiometer, Copenhagen, Denmark) as described previously.[21] The $TcPO_2$ electrodes were calibrated in room air. The probe temperature was set to 44^0C.

Procedure
Patients were placed on a couch in a comfortable supine position with the leg being measured, in a stable, relaxed position. A pneumatic tourniquet (width 18 cm) was placed around the thigh of the leg being measured. The distance between the measured skin and the LDPI was 20 cm. After an acclimatisation period of 15 minutes in a room with a constant temperature of 22 °C, measurements with LDPI were performed in a completely darkened room.
$TcPO_2$ measurements were performed under the same conditions, either 20 minutes after LDPI measurements or the next day.

FIGURE 1
Laser Doppler perfusion imager.

Venous occlusion test
The first LDPI measurement was performed in a square, measuring 36 mm x 36 mm in an almost complete AB lesion. The pneumatic tourniquet was inflated to 70 mmHg and measurements were performed after 2 and 5 minutes. The tourniquet was deflated and the last measurement was performed 30 seconds after deflation. Each measurement took 60 seconds.
Control measurements were performed in the middle of the medial side of knee at the same limb in the healthy skin of 10 patients (group A) and in 10 healthy control patients in the medial ankle region (group C). For all scans, the computer calculated the mean perfusion in millivolts (mV) and the standard deviation (SD).
The venoarteriolar response (VAR) was defined as basic resting flux (BRF) minus flux during venous occlusion (VOC) as a ratio to basic resting flux (100*(BRF-VOC): BRF).

For $TcPO_2$ measurements the tourniquet was inflated after stabilisation was reached (about 30 minutes). The tourniquet was inflated to 20, 40, 60 and 80 mmHg, for 5 minutes each.

Statistics
A Graphpad instat software package was used. Results were statistically compared using Wilcoxon's paired signed rank test, or in the case of inter group comparisons, the Mann-Whitney U test.

RESULTS

Table 1 shows details of the perfusion in millivolts in AB lesions, healthy skin in CVI patients (knee region) and in healthy controls. Median basic resting flow was significantly higher in areas with AB lesions than in healthy controls (0.67 mV versus 0.21 mV p=0.002). Median basic resting flow was also significantly higher in areas with AB lesions, than in control measurements in the knee region (0.67 mV versus 0.31 mV, p=0.008).

TABLE 1
LDPI measurements: mean (and median) perfusion in millivolts (mV) in Atrophie Blanche (AB), healthy control patients and normal skin in knee region of patients with CVI and AB before, during and direct after venous occlusion.

	AB lesions	Healthy control patients	Normal skin in knee CVI
Number of patients	16	10	10
Before venous occlusion	0.67 (0.46)	0.21 (0.20)	0.31 (0.28)
After 2 min 70 mmHg	0.25 (0.24)	0.12 (0.11)	0.19 (0.17)
After 5 min 70 mmHg	0.27 (0.25)	0.11 (0.11)	0.19 (0.18)
After venous occlusion	0.67 (0.49)	0.19 (0.20)	0.33 (0.34)

Venous occlusion with 70 mmHg of two minutes, obtained by inflating the tourniquet on the upper leg to 70 mmHg, resulted in a decrease of flux. There was a significant difference between decrease in flux of AB lesions and normal skin [table 1].

TABLE 2

The **venoarteriolar response** (VAR): basic resting flux (BRF) minus flux during venous occlusion (VOC) as ratio from basic resting flux (100*(BRF-VOC):BRF) and the **reduction in flux on venous occlusion** (VOC/BRF) in AB, in normal skin (knee region) in patients with AB, and in healthy controls.

	Normal skin knee region	Atrophie Blanche	Healthy controls
VAR	33%	58%	43%
	p=0.003		p=0.04
VOC/BRF	67%	42%	57%
	p=0.004		p=0.03

P values, compared with AB lesions

The flux did not decrease further after 5 minutes of venous occlusion. Deflating the cuff resulted in the same flux as before venous occlusion in both groups.
$TcPO_2$ resting values were significantly lower in AB lesions [table 3]. $TcPO_2$ resting values were not significantly different in patients with CVI, perilesional measurements and healthy controls. A significant decrease in $TcPO_2$ values compared with basic values occurred in AB lesions with 40 mmHg, in CVI skin with 60 mmHg and in healthy controls with 80 mmHg.

TABLE 3

Average transcutaneous oxygen values (in mmHg) in AB lesions, perilesional skin, CVI without AB lesions and healthy controls before, during and after venous occlusion

	AB lesions	Perilesional	CVI without AB	Healthy controls
Number of patients	9	9	10	10
Resting values	10.6	58.3	62.4	63.8
20 mmHg	9.4	57.7	58.9	65.1
40 mmHg	7.4 *	56.3	58.6	67.1
60 mmHg	5.1 *	53 *	55 *	62.8
80 mmHg	4.4 *	46.9 *	47.3 *	52.7 *
After	7.4	53.3	59.9	67.7

- = significant compared with resting values

DISCUSSION

Capillary microscopy, TcPO2 measurements and LDI measurements[12,13,18] can obtain information about the microcirculation. Recently, LDPI is added for microcirculatory measurements.[14] The technique of LDPI is able to produce a two-dimensional image of the cutaneous microcirculation within a specific area and does not influence the skin because there is no contact between the scanner and the skin.[19,22] Although AB is a severe complication of CVI, measurements with LDPI performed specifically in AB lesions have not been reported before. Increased basic flux in patients with CVI in general or liposclerotic skin is described[13,15-17], however nothing is known about AB.

In this study a significantly increased resting flux measured by LDPI has been measured in areas with large AB lesions in patients with CVI, compared with healthy controls (p=0.002, Mann Whitney test) and in clinical normal looking skin in patients with CVI (p=0.008, Mann Whitney test).

An increased flux measured by LDI in patients with CVI has been described previously.[13] An increased resting flux in areas with AB lesions can be explained by the morphology of AB. LDPI measures to a depth of 1-1.5 mm, where capillaries, arterioles and venules are present. In AB lesions the number of capillaries is decreased so the blood volume has to pass through a decreased number of capillaries.[23] When the number of moving erythrocytes is increased or when the velocity of blood flow is increased, an increase of flux can be expected. The same volume can only pass through a decreased capillary bed, when the velocity is increased. So other capillaries, leading to an increased basic resting flux perform the function of the occluded capillaries. In summary the increased flux could represent a decreased number of capillaries, and an increase in flow and diameter.

The increase in flux can not only be found in AB lesions but probably also around AB lesions.

As expected significantly decreased $TcPO_2$ values in AB lesions were found. $TcPO_2$ values in CVI patients (both perilesional skin and CVI patients without AB) were decreased compared with healthy controls, although this difference was not statistically significant. These data are consistent with other studies, which show non-significantly decreased $TcPO_2$ values in patients with CVI without clinical signs, whereas $TcPO_2$ values in patients with CVI with clinical signs are significantly decreased.[12,16] In our study $TcPO_2$ measurements of patients with CVI showed no clinical abnormalities: in perilesional measurements AB was avoided, while in patients with CVI, there was only mild CVI, without dermatoliposclerosis and AB.

The contradiction of increased flux and decreased $TcPO_2$ values in AB lesions can be explained as follows. $TcPO_2$ values predominantly reflect the effects caused by the capillaries (comprising a considerable part of the nutritive vessels), which are partly occluded by microthrombi and might be influenced by fibrin cuffs, trapping of leucocytes and oedema, whereas the LDPI mainly reflects the flux of blood in the deeper skin layers (which mainly serve the thermoregulation). Chronic venous hypertension may cause increased flux in the deep vessels, and because of

vasodilatation a decreased flux in the superficial vessels, which increase the risk for developing microthrombi. Bollinger suggests that AB is a result of minor skin infarctions caused mainly by CVI.[4] Decreased $TcPO_2$ values and decreased numbers of capillaries in AB support this hypothesis. Other important theories causing CVI play a role such as disturbed fibrin formation and "trapping" of leucocytes are sustained by decreased flux.[24,25]

To simulate the high walking venous pressure, that exists in patients with CVI, a venous occlusion test was used. A statistically significant difference in venoarteriolar response, and so a difference in reduction in flux on venous occlusion between AB and healthy skin was found. These data are consistent with other studies, where both Leu *et al.*[13] and Creutzig *et al.*[16] found a greater decrease in flux on venous occlusion in CVI skin than in healthy controls. Belcaro *et al.*[15] described an impaired venoarteriolar response in CVI skin, while no difference was measured in other studies.[14,26] Differences in results might be explained by the different methods used. In most studies LDF is used instead of LDPI. LDF, however, is limited in its clinical usefulness by its poor reproducibility.[14] The main disadvantages are its spatial resolution (1 mm^2), and the need to apply the probe directly to the tissue of interest.[19] LDPI has a high reproducibility and records the perfusion in a specific tissue area.[27]

In addition to different techniques, a greater reduction in flux can be expected in CVI patients, because their basic flux is much higher than in healthy controls.

In our study venous hypertension is produced in the supine position by inflating a cuff around the limb, instead of standing position. This method is described by Kuiper and Brakkée and is of proven reliability[28] and has been used in several studies.[14,17,26] Venous occlusion by a cuff applied to the thigh, results in equal pressures in the veins, causing venous occlusion with an unchanged arterial inflow.

In our study no rebound reaction after venous occlusion was seen in the LDPI measurements, neither in CVI patients, nor in healthy controls. This might be caused by the long duration of measurement (about 1 minute).

It can be concluded that basic resting flux in AB lesions measured with LDPI is increased compared with clinically normal skin and healthy controls, and that the flux is decreased more by venous occlusion in AB lesions. A strongly decreased flux on venous occlusion might lead to an increased risk in coagulation disorders of developing microthrombi and trapping of leucocytes, finally resulting in AB lesions. Because there is no rebound reaction, a lack of reserve capacity of the microcirculation is suggested.

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CHAPTER 5

THE INFLUENCE OF ARTIFICIALLY INDUCED VENOUS HYPERTENSION ON CAPILLARY FLOW IN PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY WITH AND WITHOUT ATROPHIE BLANCHE

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ABSTRACT

Chronic venous insufficiency (CVI) is known for its long term complications as a result of increased walking venous pressure in macro and microcirculation. Atrophie blanche is one of the most severe complications because of its recurrent painful and difficult to heal leg ulcers.

With the use of capillary microscopy we performed a pilot study of the skin microcirculation in atrophie blanche in the medial ankle region of 5 patients with CVI without atrophie blanche. Patients were investigated in supine position. During different venous hypertension pressure steps, induced by tourniquet inflation, a decrease in capillary blood cell velocity was seen in both groups. Venous hypertension was induced by a inflatable cuff around the thigh. There was no difference in initial capillary blood cell velocity or in reaction pattern between both groups.

Venous hypertension induced capillary flow stops or standstills; the number of standstills and the total duration of standstill increased during venous pressure steps. Long duration standstills were seen equally in both groups.

Although the efflorescencies of atrophie blanche and CVI without atrophie blanche are dramatically different, the functional alterations, observed with the capillary microscopy are the same. This suggest that different clinical signs of CVI are based on the same basic alterations of the skin microcirculation in CVI. Local factors may be responsible for the differences in skin manifestations in the cause of CVI.

Standstills and decreasing capillary blood cell velocity are probably a normal physiological reaction on venous hypertension. The importance of this phenomenon in the pathogenisis of CVI is unknown. It is possible that they form an increasing risk for the formation of microthrombi in patients with CVI, together with the known endothelial damage in capillaries and white cell trapping.

INTRODUCTION

Chronic venous insufficiency (CVI) is well known for its frequent complications of atrophie blanche, dermato- et liposclerosis and recurrent long-standing leg ulcers. As a result of venous reflux caused by valvular incompetence of deep, superficial and/or perforating veins an increased walking venous pressure is obtained.[1] The increased venous pressure in the macrocirculation is transmitted retrogradely into the microcirculation of the skin, finally resulting in changed morphology of the capillaries.[1,2] Four major theories for developing skin complications and the formation of venous leg ulcers have been put forward 1) the development of fibrin cuffs around capillaries [3], 2) intracapillary microthrombi[4], 3) white cell trapping[5], and 4) the growth factor trap hypothesis.[6] In the fibrin cuff theory it is suggested that leakage of fibrinogen from the capillaries induces a fibrin-cuff around the capillaries, leading to a diffusion barrier for oxygen and nutrients. [3] Bollinger demonstrated by using capillary microscopy that there is a reduced number of capillaries in CVI skin and suggested that this might be the result of microthrombosis.[4] In the hypothesis of white cell trapping it is suggested that, due to venous hypertension, white cells adhere (trap) to the endothelium of the capillaries which induces a release of proteolytic enzymes and superoxyde metabolites, causing destruction of the surrounding tissue. [5] Finally, it is suggested by Falanga that venous hypertension induces microtrauma of the endothelium, which results in increased capillary permeability with leakage of fibrin and macroglobulins into the dermis; these extravasated plasma proteins may trap growth factors, leading to slowly healing ulcers.[6] Neither of these theories have been fully proven until now, although it is generally accepted that probably a combination of these factors plays a role in the pathogenesis of complications of venous insufficiency. It is clear that tissue viability is threatened when nutritional circulation is.[7]

Especially in atrophie blanche lesions in CVI, there are strong indications that microthrombi occur in microcirculation. Both histological studies and capillary microscopic studies support this theory. Histologically, occlusion of capillaries in the papillary dermis is shown in atrophie blanche.[8,9] Bollinger found avascular fields and clear indications of minor skin infarctions using sodium fluorescein capillary microscopy.[4]

Up to now the effect of venous hypertension on capillary flow was, to our knowledge, only measured by Fagrell and Östergren in the nailfold capillaries of healthy individuals.[10,11] They measured both a decrease in capillary blood cell velocity and standstills during venous hypertension. The effect of venous hypertension on capillary flow in the medial ankle region of patients with CVI is unknown. Atrophie blanche is always reported by clinicans as a severe sign of CVI with a high risk factor for the development of painful and slowly healing leg ulcers.

It is unclear why in certain patients with CVI atrophie blanche will occur, while in others it will not. Is there is a difference in reaction pattern on venous hypertension in CVI patients with and without atrophie blanche? The aim of the study was to assess the effect of stepwise induced venous hypertension on capillary flow in atrophie blanche in the medial ankle area in patients with CVI, and in the medial ankle area without atrophie blanche in patients with CVI. Is there a difference in reaction pattern between these two groups of patients?

PATIENTS AND METHODS

Patients

Nine patients, 7 non-smokers (1 male, 8 females, average age 65.3 years (range 51-78), known with clinical signs of CVI with atrophie blanche (group 1) and 5 patients (2 males, 3 females, average age 68.6 years (range 65-74) with the same clinical signs of CVI without atrophie blanche (group II), all non-smokers, were selected. The severeness of CVI was determined with light reflection rheographie.[12] Mean venous refilling time was equal in both groups (8.7 versus 7.9 s). Exclusion criteria were diabetes mellitus, arterial insufficiency (ankle/arm index <0.8) and well known haemostatic disorders. Two patients were known with mild hypertension (treated).

Methods

Capillary microscopy was performed with a Wild-Leitz microscope as described before.[13] The microscope was equipped with a 10x objective (Leitz L10; numeric aperture 0.3). Incident illumination was performed using a Leitz Ploemopak system and a POL-cube; light came from a 100 Watt mercury arc. Skin transparency was enhanced by a drop of paraffin oil. The microscopic images were projected onto the sensitive surface of a video camera (Philips), and were recorded on videotape (Sony, Betamax) for off-line analysis.
In the centre of the atrophie blanche lesion one tortuous capillary was selected. In this capillary, capillary blood cell velocity was determined by the flying spot method.[13] Furthermore, the number of standstills in flow and the duration of each standstill was determined. Measurements were performed in the venous part of the capillary loop. The diameter was measured in the middle of the part of the vessel in which capillary blood cell velocity was assessed. In patients without atrophie blanche a capillary was selected in the region 5 cm above the medial ankle.

Procedure

Patients refrained from smoking and caffeine drinking during the last two hours before the measurements. All measurements were performed in a temperature controlled room (24°C) in the afternoon. Patients were placed in a comfortable supine position. The study was performed in CVI skin of the leg with and without atrophie blanche lesions, located dorsal and proximal of the malleolus medialis. In order to study the CVI skin disorders with the leg in a stable relaxed position, the

leg was restrained in a brace without influencing the microcirculation. A pneumatic tourniquet was placed around the thigh of the leg being measured. After an acclimatisation period of 15 minutes baseline recordings were made followed by venous hypertension pressure steps of 5 minutes each (congestion pressure: 20, 40, 60 and 80 mmHg). During each pressure step, measurements were performed. Measurements were performed either in the centre of the atrophie blanche lesion or about 5 cm above the medial malleolus in patients without atrophie blanche.

Statistics

Data are presented as median with their inter quartile ranges. A Graphpad instat software package was used. Results were statistically compared using Wilcoxon's paired signed rank test, or in the case of inter group comparisons, the Mann-Whitney U test. A p value of < 0.05 was considered statistically significant.

RESULTS

Results are summarised in figure 1 and table 1. All patients with atrophie blanche showed the typical glomerulus-like, enlarged capillaries [figure 2]. The patients of group II showed enlarged capillaries, although no really glomerulus-like capillaries were seen. The baseline diameter of capillaries in patients of group I was 12 ± 4 µm and in patients of group II 9 ± 6 µm. This difference was not statistically significant.

FIGURE 1

Mean capillary blood cell velocities (CBCV) in mm/s in patients with CVI with atrophie blanche (group I) and without atrophie blanche (group II).

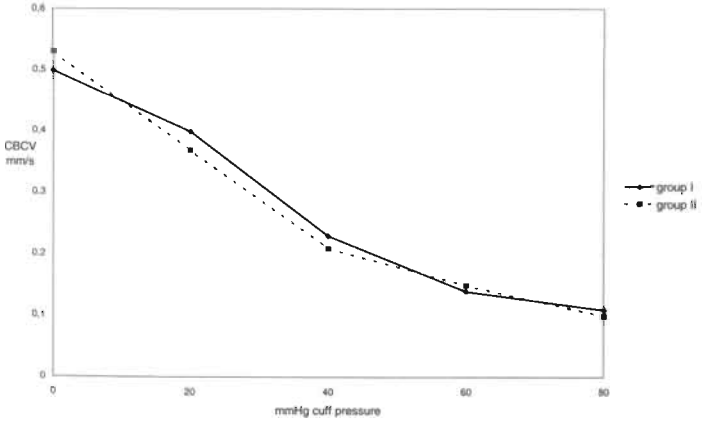


FIGURE 2
Typical glomerulus-like capillaries.

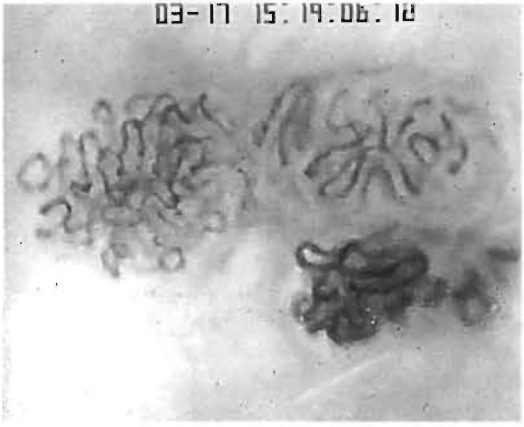


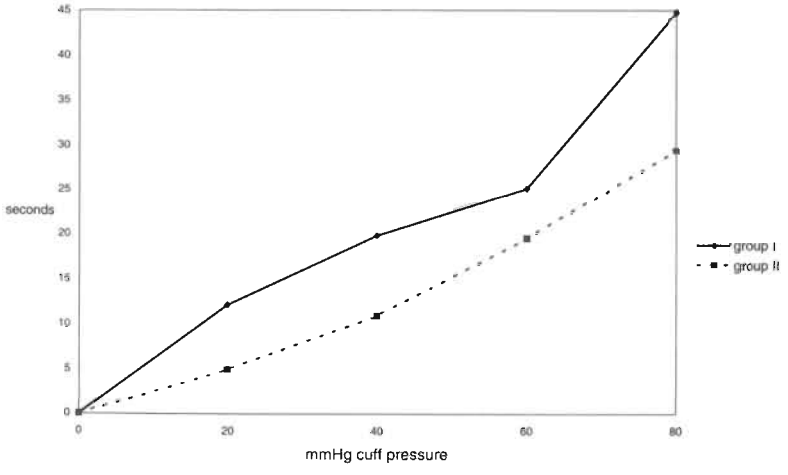
TABLE 1
Total number of standstills per minute and standstills longer than 10 seconds in 9 patients with CVI with atrophie blanche (group I) and 5 patients with CVI without atrophie blanche (group II) per minute during venous hypertension. P value represents the difference of mean number of standstills between group I and II at the same venous pressure step. Data are presented as median values (interquartile ranges).

	Group I		Group II		P value
Cuff pressure	median	> 10 s	median	> 10 s	
0 mmHg	0	0	0	0	NS
20 mmHg	0.2* (0-0.8)	0	0.2* (0.2-0.4)	0	NS
40 mmHg	1.6* (0.2-2)	0	0.4 (0.2-1.2)	0	NS
60 mmHg	1.2 (0.8-2)	0.02	0.8 (0.6-1)	0.08	$p < 0.05$
80 mmHg	1.7 (0.2-2.2)	0.70	0.7 (0.4-1.5)	0.10	NS

* Significant compared with previous venous occlusion values
NS= not significant (atrophie blanche compared with CVI)

Capillary blood cell velocity and capillary blood cell velocity before and during venous hypertension were similar in both groups [figure 1]: blood cell velocity decreased during the successive pressure steps. In almost all patients both with and without atrophie blanche flowmotion was seen at 40 mmHg and higher pressure steps.
Standstills were seen in both groups during all venous pressure steps [table 1]. An increase in number of standstills was seen during subsequent pressure steps, the increase already statistically significant at 20 mmHg. In patients of group I the number of standstills increased significantly at the pressure step from 20 to 40 mmHg, while this was not seen in group II. Although the standstills were only quantified in one capillary per patient, other capillaries exhibited a similar pattern. The number of standstills tended to be higher in the patients with atrophie blanche, although this was only statistically significant at 60 mmHg. The duration of the standstills ranged from 2 to 48 seconds. Standstills longer than 10 seconds (10-48 s) were seen in 4 out of 9 patients of group I and 3 out of 5 patients of group II. Standstills longer that 10 seconds were only seen at 60 and 80 mmHg. Standstills occurred during the whole period of venous hypertension. The total length of stop in bloodflow (number of standstills x duration of standstills) increased with increasing pressure steps [figure 3].

FIGURE 3
Total duration of standstill (number of standstills x duration) in capillaries of patients with CVI without atrophie blanche (CVI) and with atrophie blanche (AB).



DISCUSSION

Changes in capillary blood cell velocity in the medial ankle may play an important role in the aetiology of the clinical signs of CVI. Our study showed that venous hypertension, induced by an upper thigh cuff, results in a significant reduction in capillary blood cell velocity and a significant increase in number of standstills in capillaries of the skin at the ankle area of patients with CVI with and without atrophie blanche in lying position. There in no difference in reaction pattern between patients with and without atrophie blanche. There was no significant difference in the diameter of capillaries, although the diameter of capillaries in atrophie blanche showed a tendency of a larger diameter. The diameters of the capillaries were similar to the diameters measured by Stücker, who found a diameter of 10 μm for mild CVI, 16μm for atrophie blanche lesions and 8.5 μm for healthy controls.[15]

Capillary microscopy is only possible when the leg is in a stable position. This technique can be performed the best when the patient is in supine position. Patients with CVI and healthy controls are, however, only during walking different, concerning their venous haemodynamics. The key difference is the walking venous pressure. By using a horizontal pressure model, as it was developed for horizontal venous pressure measurements, we simulated the condition of walking venous hypertension.

We studied the effect of stepwise increase in venous pressure, while most studies, determining the effect of venous hypertension on the microcirculation, assess changes at one level of venous hypertension. This is more reliable since venous hypertension is not continuously stable. The reduction in capillary blood cell velocity appears to be almost linearly dependent on the applied pressure of the upper thigh cuff. At 40 mmHg a kink in this line is seen and capillary blood cell velocity decreases less than would have been seen in a complete linear response. This pattern is seen in both groups of patients.

There are several theories explaining a decrease in capillary blood cell velocity during venous pressure such as the venivasomotor reflex and the myogenic autoregulation. It is also possible that the decrease in perfusion pressure itself causes a decrease in blood cell velocity. A loss of postural vasoconstrictor reflex might cause the kink in decrease in capillary bloodcell velocity. Luetolf suggested a loss of postural vasoconstrictor reflex in patients with CVI when he studied the difference in perfusion of capillaries in the medial ankle region of healthy volunteers and of patients with CVI.[16] He found a capillary under perfusion in patients with CVI. A reduction of capillary perfusion during venous pressure was seen in healthy controls and not in patients with CVI. Weindorf demonstrated a dilatation in capillary vessels during sitting and standing position.[17]

The efflorescencies of patients with and without atrophie blanche is dramatically different. Since the functional alterations observed with capillary microscopy are the same, it is suggested that the clinical signs of CVI are based on the same basic alterations of the skin microcirculation. Local factors as disturbed fibrinolysis, extravasation of erythrocytes and extra cellular matrix, will be responsible for the difference in skin manifestations the course of CVI. Atrophie blanche is only a

clinical entity correlated to be a more severe stage than CVI without atrophie blanche.

In the present study all patients but one showed capillary standstills as a result of venous hypertension. The higher the venous pressure, the more standstills were seen. Standstills longer than 10 seconds were only seen in 7 of the 14 patients, at venous pressures of 60 and 80 mmHg.

The origin, importance and complications of these standstills are unclear. This study shows no difference in reaction pattern in patients with or without atrophie blanche. Standstills might be a first event for developing microthrombi or standstills might be the result of microthrombi. Standstills are probably a normal physiological reaction on venous hypertension, since they are both seen in nailfold capillaries of healthy controls and in the medial ankle region.

The total duration of standstill of the blood during venous pressure is relatively high at higher venous pressure steps. Patients with CVI have a continuously increased venous pressure during the day, and so probably a long duration of standstill in flow will occur compared with healthy controls. It has been well demonstrated that the fibrinolysis in patients with varicose veins and/or CVI is decreased and that the fibrinolytic function of capillary endothelium of these capillaries is diminished, adding a potential synergistic effect to the increased standstills.[18,19] Especially in atrophie blanche lesions there are strong indications that microthrombi are caused by local coagulation disorders and impaired fibrinolysis, which may be partly based on diminishing flow, partly on yet unknown mechanisms. Standstills of the blood by themselves can be, according to Virchow, a luxating moment for thrombosis. In addition, it is known that during venous hypertension leucocytes adherence to the endothelial cells, and release toxic oxygen metabolites and proteolytic enzymes, resulting in damage to the capillaries; this might contribute to the increase in the standstills.[5] Standstills in capillaries in the medial ankle region area may therefor form an increased risk in patients with CVI. There are circumstantial evidence for the hypothesis of microthrombi. The role of white cell trapping is less clear.

It would be interesting to study the difference in reaction pattern at the medial ankle of patients with and without CVI. In this region, however, capillaries of healthy controls are hard to study because only small comma shaped dots are seen.

The effect of venous hypertension on blood cell velocity in capillaries in nailfolds of healthy control has been studied by Fagrell and Östergren.[10,11] In the study of Östergren *et al.* venous hypertension (50 mmHg) induced a decrease in blood cell velocity in nailfolds capillaries to 14% (from 0.59 to 0.08 mm/s).[10] Fagrell and his group studied the effect of 7 minutes of venous pressure (40 mmHg) in blood cell velocity in nailfold capillaries of 7 healthy volunteers.[11] They found a basic blood cell velocity of 0.39 mm/s, which decreased to 30%, (to 0.12 mm/s) during venous pressure. The differences in basic capillary blood cell velocity may be explained by measurements in different parts of the capillary, however, both above mentioned studies did not state in which part of the capillary loop measurements were performed. In our study measurements were performed in the venous part of the capillary loop. It must be realised, however, that venous and arterial loops are

hard to distinguish since the capillaries in this area in patients with CVI are glomerulus like. In the above mentioned studies, as in our study, only one capillary was studied.
The smaller decrease in capillary blood cell velocity during venous pressure in our patients (43% at 40 mmHg and 35% at 50 mmHg) may be explained by a combination of increased resistance of the vessel wall of capillaries and a diminished postural vasoconstrictor reflex in patients with CVI.
It is hypothesised that increased venous pressure probably causes several events like damage of the endothelium, decreased fibrinolysis, sludge formation, standstills of blood flow and white cell trapping. These facts together might result into increased platelet aggregation and finally the formation of microthrombi.
It is concluded that patients with CVI with and without atrophie blanche show a diminishing capillary flow during venous hypertension, together with an increasing number of standstills. Both a diminishing capillary flow and a increasing number of standstills, together with other events like a decreased fibrinolytic function of capillary endothelium, will form an increasing risk for the formation of microthrombi in patients with CVI. A similar etiological factor in patients with CVI with and without atrophie blanche is suggested. Local factors are probably the cause for the differences in clinical appearance. Further studies with healthy controls and CVI patients with and without atrophie blanche are necessary.

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CHAPTER 6

THE PREVALENCE OF FACTOR V LEIDEN MUTATION IN PATIENTS WITH LEG ULCERS AND VENOUS INSUFFICIENCY

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ABSTRACT

Objective
To study the prevalence of factor V Leiden mutation in patients with chronic venous insufficiency and venous leg ulcers, compared with a control group and to find out whether factor V Leiden mutation is more frequent in patients with chronic venous insufficiency and a positive history of deep venous thrombosis.

Design
A case control study.

Setting
Three outpatient dermatological clinics.

Patients
A total of 92 patients (37 men, 55 women) with venous leg ulcers and 53 control patients (23 men, 30 women).

Main Outcome Measures
Factor V Leiden mutation.

Results
Factor V Leiden mutation was significantly more frequent in patients with chronic venous insufficiency and venous leg ulcers than in the control group (23% versus 7.5%, p=0.03), and the patients with factor V Leiden mutation were more likely to have a history of venous thromboembolism (91% versus 48%, p=0.002). Also recurrent deep venous thrombosis (38% versus 14%) and recurrent leg ulcers (9 episodes or more) occurred more frequently in the patients with factor V Leiden mutation (43% versus 19%, p=0.01). No difference was observed in venous refill time, or in the presence of dermatoliposclerosis and atrophie blanche.

Conclusions
Factor V Leiden mutation is more frequent in patients with venous leg ulcers than in the control group and the general population. Patients with factor V Leiden mutation have an increased risk of developing deep venous thrombosis and recurrent leg ulcers.

INTRODUCTION

Venous leg ulceration is a significant health problem for both patients and clinicians. It forms the end stage of the complex of symptoms of chronic venous insufficiency (CVI). Epidemiological studies have estimated the prevalence of severe CVI to be between 6 and 8%, whereas 0.5 to 2% of the general population is affected by venous leg ulcers.[1,2,3]

In 50% of patients with leg ulcers a history of deep venous thrombosis (DVT) is seen.[4] In this group of patients the diagnosis of venous thrombosis has often been based on "clinical signs and symptoms". Only a limited percentage of patients suspected of DVT really had the disease. Their proportion is dependent on referral and selection.[5,6]

Activated protein C (APC) resistance, as a frequently occurring hereditary risk factor for DVT, was first described by Dahlbäck *et al.* in 1993.[7] One year later the genetic defect, known as factor V Leiden mutation, was identified by Bertina *et al.*[8] The prevalence of the factor V Leiden mutation is estimated to be 5 to 6% in the general population in Europe,[9,10] and 3 to 5% in the Netherlands.[11,12]

The activated form of coagulation factor V (Va) plays an important role in the generation of thrombosis. To prevent excessive thrombus formation factor Va is inactivated by APC. This efficient negative feedback mechanism is disturbed in patients with factor V Leiden mutation because the mutation is located on one of the major APC-cleavage sites, leading to so called APC resistance.

Heterozygous factor V Leiden mutation increases the risk of venous thrombosis 5-7 fold. APC resistance accounts for 20% of the cases of DVT's, and for 50% of familial venous thrombosis.[11,13,14] Leg ulcers represent one of the most serious complications of the postthrombotic syndrome.

For screening APC resistance, functional coagulation tests, such as determination of activated partial thromboplastin time, can be used. The gold standard is polymerase chain reaction analysis of genetic DNA.[13,15]

The aim of this study was to investigate:

a) the prevalence of factor V Leiden mutation in a large group of patients with CVI and venous leg ulcers;
b) whether factor V Leiden mutation is seen more frequently in patients with CVI, with or without a history of DVT;
c) whether the prevalence of factor V Leiden mutation in our group of patients is higher than in the general population or in the control group.

PATIENTS AND METHODS

Patients

During an 8 month period, 92 patients (37 men, 55 women, age range 38-97 years) from the outpatient dermatological clinic of the University Hospital Maastricht, the Hospital De Tjongerschans in Heerenveen and Canisius Wilhelmina Hospital in Nijmegen were studied. All patients were treated for venous ulcers, classified as

Widmer stage III (active venous ulcer or history of recurrent venous ulcer).[1] The exclusion criteria was severe arterial insufficiency (ankle/arm index < 0.6).
As a control group 54 patients (age- and sex-matched) with isolated nonmetastasized nonmelanoma skin malignancy (basal cell carcinoma and squamous cell carcinoma) without a history of venous leg ulcers were studied. Informed consent was obtained from all patients.

TABLE 1
Data of characteristics of 92 patients with venous leg ulcers. Data are presented in mean values (ranges).

Sex	Mean age (years)	Total of ulcers in past	LRR (seconds)	History of VTE	Number of pat
Men	63.5 (38-90)	5.6 (1-20)	8.2 (4-20)	22 (10>1x)	38
Women	71.6 (48-97)	6.3 (1-20)	9.2 (4-20)	31 (4>1x)	54

VTE = deep venous thrombosis or pulmonary embolism.
LRR indicates venous refilling time (light reflex rheography)

Methods
A detailed history of venous thromboembolism (VTE) and leg ulcers was obtained in all selected patients. The presence of clinical abnormalities, such as dermatoliposclerosis, atrophie blanche and haemosiderine pigmentation were noted. Light reflex rheography was performed as described by Neumann and Boersma.[16] A venous refill time of 20 seconds or less was considered abnormal. The characteristics of the patients are listed in table 1.
The difference in the prevalence of factor V Leiden mutation between the patients and the control group of patients was investigated.
DNA was isolated from peripheral blood leukocytes by standard methods.[5] The relevant region of exon 10 of the factor V Leiden gene was amplified by polymerase chain reaction. After amplification and subsequent digestion, the products were visualised on 2.5% agarose gels.[5]

Statistics
The results were statistically compared with those of Student T tests, Mann-Whitney and Chi-square tests. Confidence intervals (CIs) were calculated according to the method especially for case control data, on the basis of a binomal distribution.[17]

RESULTS

Twenty-one of the 92 patients showed factor V Leiden mutation, 20 patients with a heterozygous pattern and 1 patient with a homozygous factor V Leiden mutation [table 2]. The difference of prevalence in men (32%) and women (16%) was not significant.

TABLE 2

	Patients	Controls
Age (years)	68.3	65.9
FV Leiden mutation	23 %	7.5 %

In the control group of 53 patients (30 women, 23 men, average age of 65.9 years) factor V Leiden mutation was detected in 4 patients [table 3]. Factor V Leiden mutation was seen significantly more often in the group of patients with leg ulcers than in the control group (p=0.03, chi square, odds ratio, 95% CI 1.17-11.19).
In patients with factor V Leiden mutation, a history of VTE was more frequent (91% versus 48%, p=0.002, chi square). A history of recurrent DVT was seen in 8 (38%) of 21 patients with factor V Leiden mutation and in 10 (14%) of 71 patients without factor V Leiden mutation (p=0.03, Odds ratio 3.8, 95% CI 1.24-11.32). Factor V Leiden mutation was associated with an increased prevalence of venous leg ulcers, ulcers during 9 episodes or more was seen in 43% in patients with Factor V Leiden and in 19% in patients without the mutation (p=0.011, Odds ratio 4, 95% CI 1.39-12.03). There was no association between recurrent DVT and the number of recurrences of leg ulcers or between factor V Leiden mutation and the presence of atrophie blanche or dermatoliposclerosis.
The average age of the patients with factor V Leiden was not different from that of the other patients. The average venous refill time was the same in both groups (8.9 s versus 8.7 s).

TABLE 3
Prevalence rates of (recurrent) VTE, number of leg ulcers and clinical characteristics in patients with venous leg ulcers, with (group 1) and without (group 2) factor V Leiden mutation

	Group 1	Group 2
Number of patients (M/F)	21 (12/9) (23%)	71 (25/46) (77%)
History of VTE (M/F)	19 (11/8) * (91%)	34 (11/23) (48%)
History of recurrent VTE	8 ** (38%)	10 (14%)
Average age	65.0 years # range (39-97)	69.2 years range (38-90)
Number of leg ulcers in past	7.0 # range (1-20)	5.8 range (1-20)
Patients with >9 ulcers in past	9 *** 43%	11 16%
Light Reflex Rheography	8.9 s # range (4-19)	8.7 s range (4-20)
Atrophie Blanche	17 (2 unknown) # (81%)	52 (8 unknown) (73%)
Dermato- et liposcle - rosis	10 (2 unknown) # (48%)	42 (13 unknown) (59%)

Not significant in both groups
* Significant difference in patients with and without factor V Leiden mutation, p= 0.002
** Significant difference in patients with and without factor V Leiden mutation, p= 0.03
*** Significant difference in patients with and without factor V Leiden mutation, p= 0.01

VTE = deep venous thrombosis or pulmonary embolism

DISCUSSION

Chronic venous insufficiency (CVI) resulting in leg ulcers has a large impact on quality of life.[18] The present study shows a significantly increased prevalence of factor V Leiden mutation of 23% in patients with venous leg ulcers, compared with a prevalence of 7.5% in the control group (p=0.03, chi square). Our study results confirm the recently reported APC resistance rate of 26% in patients with venous leg ulcers.[19] In the study by Munkvad *et al.* gene mutations were not investigated. Another study by Grossman *et al.*, found a much lower prevalence of factor V Leiden mutation (7.7%). However, their patient group was rather small (26 patients).[20] These differences clearly show the importance of DNA analysis in confirming the diagnosis of factor V Leiden mutation.

In our study patients with a history of venous thromboembolism (VTE) were found mostly in the mutated factor V Leiden patient group. These results suggest that patients with the combination of VTE and factor V Leiden mutation have an increased risk of developing venous leg ulcers. However, the fact that the clinical history with respect to DVT is not always reliable, should be taken into consideration. In the past, duplex sonography was not available, and other techniques, such as phlebography and impedance plethysmography, were certainly not routinely used in all cases. To date, there are at this moment no additional diagnostic procedures, such as photoplethysmography, which is an accepted screening method for the haemostatic consequences of CVI, to predict increased risk for leg ulcers, since venous refill time was the same in both patient groups.

The association between recurrent leg ulcers of more than 9 episodes and factor V Leiden mutation indicates that the presence of factor V Leiden mutation represents a high risk for recurrent venous ulcers.

Recurrent venous thrombosis was three to four times more frequent in the group of patients with factor V Leiden mutation. These data support the hypothesis that patients with factor V Leiden mutation may require prolonged anticoagulation therapy, as suggested by Ridker *et al.*[10] They reported a four- to fivefold increased risk of recurrent venous thrombosis in patients with factor V Leiden mutation,[21] whereas others did not observe such an increased risk.[22]

As a control group patients with solitary uncomplicated skin malignancies were studied. Although these individuals do not represent the "healthy" population, no increased prevalence of DVT is seen in this group of patients, opposed to patients with internal or metastasised malignancies.[23] It should be taken into account that the patients with CVI seen by us in the outpatient clinic are patients with more severe complications; they might not be representative of all patients with venous leg ulcers.

Beside venous thrombosis in macrocirculation, microthrombi in microcirculation are thought to play an important role in the pathogenesis of venous leg ulcers.[24] It is not unlikely that during ulceration microthrombi are formed and that thrombotic events in macrocirculation and in microcirculation are related. The high percentage of factor V Leiden mutation in patients with venous leg ulcers supports this theory.

The role of compression therapy and anticoagulation in preventing postthrombotic complications should be considered. The importance of compression therapy for two years after DVT has been diagnosed, has recently been demonstrated.[25] The rate of postthrombotic syndrome was reduced by 50% by the use of compression stockings.
Lower rates of recurrent idiopathic DVT during 6 months of oral anticoagulant therapy instead of 6 weeks support the hypothesis that patients with DVT and factor V Leiden mutation may require an increased period of anticoagulant therapy.[26] Long-term aspirin therapy in the group of patients with recurrent leg ulcers might decrease the risk of recurrent ulcers.[27] Additional trials of low-molecular weight heparin and aspirin are necessary to study the reduction of these postthrombotic complications.
We conclude that factor V Leiden mutation is more frequent in patients with (recurrent) venous leg ulcers than in the general population. Patients with a factor V Leiden mutation have an increased risk of developing DVT and recurrent venous leg ulcers. Further studies with prolonged anticoagulant and compression therapy are necessary to decrease the risk of VTE and postthrombotic complications.

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CHAPTER 7

THE INFLUENCE OF LOW MOLECULAR WEIGHT HEPARIN IN THE TREATMENT OF ATROPHIE BLANCHE

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ABSTRACT

Low molecular weight heparins (LMWH) have become increasingly popular since they have proven to be both safe and effective for the prophylactics and treatment of venous thromboembolism. They are often used in the treatment of venous leg ulcers. The effect of LMWH on the skin microcirculation of patients with CVI is unknown.

With the use of capillary microscopy, laser doppler perfusion imager (LDPI) and transcutaneous oxygen ($TcPO_2$) measurements the influence of LMWH during 10 weeks was studied in patients with CVI with atrophie blanche. Measurements were performed on atrophie blanche lesions. Both basic values and the reaction pattern on venous hypertension steps (20, 40 and 60 mmHg) were studied.

No statistically differences were found in $TcPO_2$ measurements, LDPI measurements, capillary blood cell velocity and number of standstill in capillaries. Also the reaction pattern on venous hypertension did not improve after treatment. A possible explanation may be that in venous legs without active ulcers, a stable situation is created, in which the effects of LMWH is not measurable.

Further studies are necessary to assess whether or not LMWH will improve the microcirculation and therefor the healing rate of leg ulcers, and whether LMWH are useful in the prevention of leg ulcers in patients with CVI and atrophie blanche.

INTRODUCTION

Chronic venous insufficiency (CVI) and the resulting leg ulcers have a considerable impact on quality of life.[1] Epidemiological studies have estimated the prevalence of severe CVI to be between 6 and 8%. Venous leg ulcers affect 0.5 to 2% of the general population.[2-4]

Venous thrombosis play often a role in the pathogenesis of CVI. Venous thrombosis causes valvular destruction, which results in venous reflux, leading to CVI. In the pathogenesis of leg ulceration, not only the macrocirculation seems to be important, but also disturbances in the microcirculation. Based on capillary microscopic findings, Bollinger hypothesised that local microthrombi are likely to play an important role.[5] These findings are confirmed by histological findings in patients with venous insufficiency and ulcers in which occluded vessels are seen in the papillary dermis. In atrophie blanche lesions recurrent ulceration is more often seen than in patients with chronic venous insufficiency without atrophie blanche.[6]

Many therapies have been used in the treatment of leg ulcers, with varying results. The combination therapy of phenformin and ethylestrenol was very successful in the treatment of leg ulcers.[7,8] Five patients treated by Gilliam showed relief of pain by the third or fourth week of treatment and had progressive healing of all lesions. Most patients remained asymptomatic on this combination treatment.[7] In another study ten patients were treated for 1 to 12 years; longstanding ulcers healed within 4 to 8 weeks, pain decreased within 7 days and new lesions decreased in frequency and then no longer apperaed.[8] The effect of the combination of ethylestrenol and phenformin is probably due to an increasing release and synthesis of plasminogen activator, which results in improved fibrinolytic activity.[7,9,10] However, in 1977 phenformin was removed from the general market by FDA decision because of its side-effects. Since ethylestrenol alone is not effective, other drugs are suggested by Jetton and Heine to be used as a substitute for phenformin and ethylestrenol, such as low molecular weight heparin (LMWH).

LMWH's have become increasingly popular since they have proven to be both safe and effective for the prophylaxis and treatment of venous thromboembolism.[11,12] Beside their safety and efficacy, LMWH's have practical advantages; because of their predictable anticoagulant effect there is no need for laboratory monitoring or intravenous infusion and they can be prescribed 1 or 2 times a day subcutaneously, also on an out patient base.[13,14]

In addition to anticoagulant properties, LMWH's have many other properties, which include increasing fibrinolytic activity and suppression of inflammation and cell mediated immunity.[15-18]

Beside their use in the treatment of thromboembolism, LMWH are prescribed in treatment of leg ulcers.[18-24] Most leg ulcers occur in patients with venous insufficiency.[25] About 30-50% of venous leg ulcers is caused by venous thrombosis.[26]

The aim of this pilot study was to investigate if 10 weeks of LMWH's might improve the skin microcirculation in atrophie blanche lesions. Alterations in

microcirculation were assessed with transcutaneous oxygen ($TcPO_2$) and laser Doppler perfusion imager (LDPI) measurements to determine the thermoregulartory blood flow, and with capillary microscopy to quantify the nutritive blood flow. Both the effect on capillary blood cell velocity and number of standstills in blood flow during venous hypertension were studied.

PATIENTS AND METHODS

Patients

Ten women known with atrophie blanche were selected from the outpatient clinic of the University Hospital of Maastricht. Chronic venous insufficiency was determined by venous refilling time (<20 s). Exclusion criteria were arterial insufficiency (ankle arm index below 0.8), diabetes, hypertension, obesity, systemic diseases or the use of anticoagulants. Mean age was 55.6 years (range 32-73). Mean number of total ulcer's in atrophie blanche lesions in the past was 3.6 (range 2-10).

Methods

Patients were treated during 10 weeks with LMWH (Clivarin, Knoll, Ludwigshaven, Germany, 1750 IU), subcutaneously, once a day. Before the study and after the 10 weeks treatment period capillary microscopy, LDPI and $TcPO_2$ measurements were performed in order to evaluate the effectiveness of LMWH.

Capillary microscopy was performed with a Wild-Leitz microscope as described before.[27,28] The microscope was equipped with a 10x objective (Leitz L10; numeric aperture 0.3). Incident illumination was performed using a Leitz Ploemopak system and a POL-cube; light came from a 100 Watt mercury arc. The microscopic images were projected onto the sensitive surface of a video camera (Philips). The microscope images were recorded on videotape (Sony, Betamax) for off-line analysis. Skin transparency was enhanced by a drop of paraffin oil. For analysis the number of standstills in flow in one capillary in atrophie blanche per patient and the duration of standstills were determined. Capillary blood cell velocity was determined by the flying spot method.[29,30] Furthermore, the number of standstills in flow and the duration of each standstill was determined. Measurements were performed in the venous part of the capillary loop.

LDPI measurements were performed with the PIM.Lisca version 2.4 (Linköping, Sweden). A full description of the laser Doppler together with evaluation of the laser-technique is presented elsewhere.[31,32] The images of LDPI are displayed with colours representing a scale of mean blood velocity.[33]

Transcutaneous oxygen tension ($TcPO_2$) was measured as described earlier.[34,35] $TcPO_2$ were assessed with the TCM-2 (Radiometer, Copenhague, Denmark). The $TcPO_2$ electrodes were calibrated in room air. The core temperature was set to 44^0C. Constant registration of $TcPO_2$ values occurred during the procedure.

PROCEDURE

Patients refrained from smoking, eating and caffeine drinking two hours before measurements. All measurement were performed in a temperature controlled room (24°C) in the afternoon. Patients were placed in a comfortable supine position. The leg was restrained in a brace, without influencing the skin microcirculation. A pneumatic tourniquet was placed around the thigh of the leg being measured.

After an acclimatisation period of 15 minutes baseline recordings were made with the capillary microscopy in the atrophie blanche lesions, followed by venous occlusion pressure steps of 5 minutes each (20, 40 and 60 mmHg). In the centre of the atrophie blanche lesion one tortuous capillary was selected in which capillary blood cell velocity, the number of standstills in flow and the duration of each standstill was determined. Measurements were performed at each venous pressure step measurements.

After another period of 15 minutes, LDPI measurements were performed in a completely dark room. The distance between the measured skin and the LDPI was 20 cm. The first measurement was performed on a square skin section (36 mm x 36 mm) in an almost complete atrophie blanche lesion; subsequent measurements were performed at the same site after 2 and 5 minutes after inflating the tourniquet to 20, 40 and 60 mmHg for 5 minutes each. The last measurement was performed 30 seconds after deflation. Each measurement took 60 seconds. For all scans, the mean perfusion in millivolts (mV) and the standard deviation (SD) were calculated by the computer. The venoarteriolar response (VAR), which was determined for each venous pressure step, was defined as the ratio of the basic resting flux (BRF) minus the flux during venous occlusion (VOC) and the basic resting flux (BRF-VOC):BRF).

Finally, $TcPO_2$ measurements were performed in atrophie blanche lesions, before as well as during the various venous occlusion steps. After stabilisation period of about 30 minutes, the tourniquet was inflated to 20, 40 and 60 mmHg for 5 minutes each.

Statistics

A Graphpad instat software package was used. Results were statistically compared using Wilcoxon's paired signed rank test. A p value of <0.05 was considered statistically significant.

RESULTS

Capillary blood cell velocity showed a tendency to increase as a result of LMWH, before as well as during the different venous occlusion steps, but the difference was again not statistically significant. Standstills in capillary flow in reaction to venous hypertension decreased after treatment with LMWH [table 1]. This difference was, however, not significant. Total duration of standstills (number of stops x duration) did not decrease significantly [figure 2].

FIGURE 1
Mean capillary blood cell velocity in mm/s in atrophie blanche, before and after 10 weeks of treatment with LMWH.

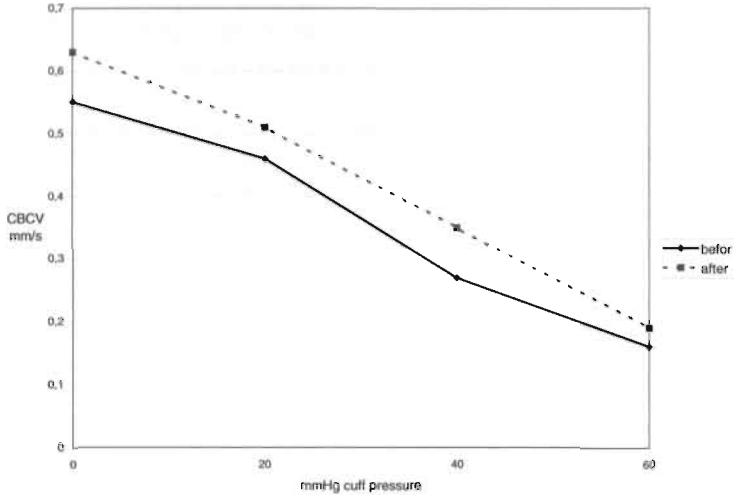

TABLE 1
Number of standstills per minute in capillaries before and after 10 weeks of treatment with LMWH. Measurements were performed at different venous occlusion steps of 5 minutes each in atrophie blanche. No statistically significant changes were observed as a result of treatment. Data are presented as median values (interquartile ranges)

VENOUS OCCLUSION PRESSURE	BEFORE	AFTER
0 mmHg	0 (0-0)	0 (0-0)
20 mmHg	0 (0-0)	0 (0-0)
40 mmHg	0.8 (0-1)	0 (0-0.5)
60 mmHg	1.6 (0.6-3.9)	0.4 (0-0.9)

FIGURE 2
Total duration of standstill in blood flow (number of standstills x duration) during 5 minutes in atrophie blanche, before and after 10 weeks of treatment with LMWH.

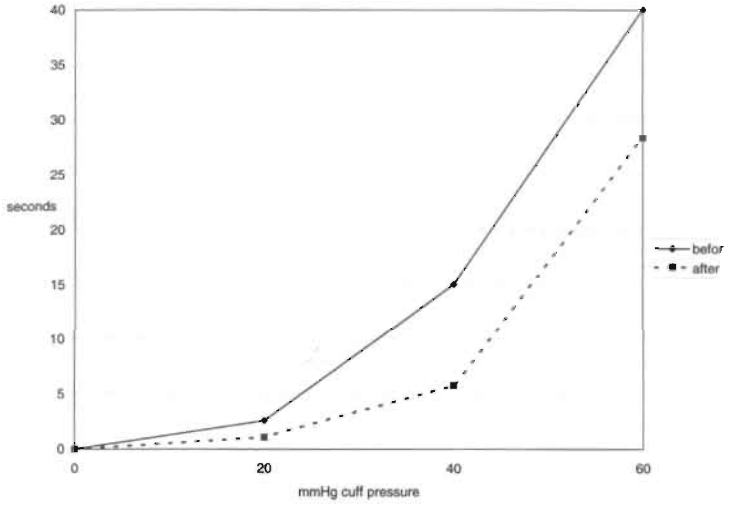

Table 2 and 3 show data of the thermoregulatory perfusion and the venoarteriolar response respectively in atrophie blanche lesions in reaction to venous hypertension before and after treatment with LMWH. Median resting flow was not influenced significantly. This also holds for the decrease in perfusion that was observed during the venous pressure steps. VAR seemed to improve during treatment, although this effect was not statistically significant.
Transcutaneous oxygen values did not improve significantly after treatment with LMWH, before as well as during the venous occlusion pressure steps [table 4].

TABLE 2
LDPI measurements: thermoregulator skin perfusion in millivolts (mV) in atrophie blanche lesion before and after 10 weeks of treatment with LMWH. Measurements were performed before, during and after venous occlusion steps of 5 minutes each. Data are presented as median values (interquartile ranges). No changes were observed as a result of treatment.

VENOUS OCCLUSION PRESSURE	BEFORE LMWH	AFTER LMWH
0 mmHg	0.33 (0.20-0.41)	0.33 (0.20-0.51)
20 mmHg	0.25 (0.19-0.34)	0.35 (0.19-0.47)
40 mmHg	0.16 (0.08-0.14)	0.18 (0.11-0.28)
60 mmHg	0.08 (0.04-0.14)	0.18 (0.08-0.22)
After	0.26 (0.17-0.37)	0.35 (0.20-0.50)

TABLE 3
The venoarteriolar response (VAR) before and after 10 weeks of treatment with LMWH. The VAR is defined as the ratio of the basic resting flux (BRF) minus flux during venous occlusion (VOC) and the basic resting flux (100*(BRF-VOC):BRF). No significant changes were observed as a result of the treatment. Data are presented as median (interquartile ranges)

VENOUS OCCLUSION PRESSURE	BEFORE LMWH	AFTER LMWH
VAR 20 mmHg	16 (10-24)	9 (0-15)
VAR 40 mmHg	55 (40-71)	46 (42-53)
VAR 60 mmHg	80 (60-88)	61 (54-72)

TABLE 4
Transcutaneous oxygen measurements (in mmHg) in atrophie blanche before and after 10 weeks of treatment with LMWH. No statistically significant changes were observed as a result of treatment. Data are presented as median (interquartile ranges).

VENOUS OCCLUSION PRESSURE	BEFORE LMWH	AFTER LMWH
0 mmHg	12 (6-25)	11 (6.8-21.3)
20 mmHg	10 (7-26)	12.5 (8-19.8)
40 mmHg	7 (5-21)	13.5 (7.3-19)
60 mmHg	5 (4-25)	13.5 (3.8-19)

DISCUSSION

In this pilot study we assessed the effect of LMWH (Clivarin) on the microcirculation in atrophie blanche lesions in patients with CVI. LMWH administration for 10 weeks did not improve resting transcutaneous oxygen values or thermoregulatory perfusion levels. The changes in resting transcutaneous oxygen values and thermoregulatory perfusion levels in reaction to increasing venous pressure were not affected either, although the venoarteriolar response tended to increase. Nutritional skin microcirculation seemed to improve during treatment with LMWH since the number of standstills and the total duration of standstill in capillary flow during venous hypertension showed a tendency to decrease and the capillary blood cell velocity was slightly higher at the end of the treatment period. To our knowledge, until now, no objective measurements are performed to study the influence of heparin on the microcirculation in patients with CVI.

No decrease in number of standstills was found as a result of LMWH treatment, neither did the total duration of standstill in capillary flow decrease significantly. It can be imagined that if standstills are a normal physiological phenomenon, the total duration of standstill in capillary flow would decrease during treatment with LMWH's. Especially on long standstills (longer than 10 seconds) this effect might occur. In our group of patients, however, only 2 long standstills before treatment and 1 long standstill after treatment (during 60 mmHg cuff pressure) were seen. Probably the group of patients studied should be larger to evaluate whether this effect of LMWH's might occur. Also a cuff pressure of 80 mmHg would more likely to show an decrease of standstill in capillary flow after treatment. Patients

with CVI have a continuously increased venous pressure (between 60 and 100 mmHg) during the day and so an effect of LMWH's may occur in this group of patients.

Standstills in capillary flow during venous hypertension have been reported before.[36,37] They may play an important role in the pathogenesis of CVI. It is unclear whether microthrombi develop due to standstills in capillary flow or that the standstills occur as a result of local microthrombi. Particularly in atrophie blanche, the hypothesis of microthrombi in the microcirculation, as suggested by Bollinger[5], is likely to play an important role in the pathogenesis.

A possible explanation that no significant improvement was found in $TcPO_2$ and LDPI measurements maybe due to the fact that a treatment period of ten weeks was not long enough to influence the skin microcirculation, or that the group studied was too small. Another reason maybe that the patients, which we studied, had no active ulceration but a stable situation of the microcirculation in the leg, with only limited signs of inflammation. In patients with ulcers inflammation plays an important role, and maybe in that period there are changes in capillary blood flow, with an increase in standstills. In patients with ulcers, improvement in the microcirculation might be found during treatment with LMWH. The tendency of a decrease in total duration of standstill in capillary flow during LMWH treatment, which was found in the present study, may contribute to an improvement in the healing of venous leg ulcers or decrease the risk or developing leg ulcers. Also the role of LMWH in the suppression of inflammation and cell mediated immunity might be of more importance in all patients with active ulcers than in a stable situation. The result of treatment with LMWH in ulcers in atrophie blanche, in which good wound healing was found, with a very good quality of the skin, support this hypothesis.[20] We were, however, not able to assess the effect of LMWH's in microcirculation, although there was a tendency of improvement in microcirculation.

Several studies show improvement in wound healing with LMWH.[18-22] Unfortunately these studies are not placebo-controlled. In one study with LMWH treatment of foot ulcers in diabetic patients an improvement in capillary circulation was found.[18] In this study LDI fluxmetry was unchanged in all patients, while the nutritive microcirculation, as quantified by capillary microscopy increased in 7 out of 9 patients. Improvement in nutritive microcirculation in above mentioned study was determined by the morphology of capillaries. No capillary blood cell velocity or standstills were measured. In the present study no capillary density was measured, because in atrophie blanche avascular fields are seen, together with glomerulus-like capillaries, measurements of capillary density or percentage of "normal" capillaries might not be reliable.

Recurrent leg ulcers and deep venous thrombosis are more often seen in patients with factor V Leiden mutation than in healthy controls.[38] LMWH's play an important role in the prevention of deep venous thrombosis.[11,12] A relation between thrombosis in veins of the macrocirculation and capillaries in microcirculation may exist. In case of a connection between thrombosis in macro- and microcirculation, treatment with LMWH might decrease the risk on the recurrence rate of leg ulcers in patients with recurrent leg ulcers and factor V

Leiden mutation. Further studies are necessary to prove the use of LMWH in treatment and prevention of leg ulcers.
It is concluded that 10 weeks of LMWH treatment does not influence the skin microcirculation in atrophie blanche, although there is a tendency of improvement. Further studies are necessary, to objectivate the effect of LMWH treatment on the microcirculation of CVI skin and on healing- and recurrence rate of venous leg ulcers and on the prevention of leg ulcers.

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CHAPTER 8

GENERAL DISCUSSION AND SUMMARY

GENERAL DISCUSSION AND SUMMARY

CLINIC

Atrophie blanche or white atrophy is described in association with several diseases. Extensive research of literature shows, however, that it can only be associated with a few internal diseases, such as scleroderma and systemic lupus erythematodus (chapter 2). Even in these diseases atrophie blanche is not really frequently reported. An incidence of less than 1 percent seems reasonable. The name atrophie blanche or white atrophy is preferred to livedo vasculitis.
Most frequently atrophie blanche is seen in patients with chronic venous insufficiency (CVI). Clinically no difference can be made, between these two forms of atrophie blanche, except that atrophie blanche as symptom of CVI is always seen on the leg, while atrophie blanche as symptom of internal disease can be seen on any part of the body.
CVI is a complex of symptoms caused by insufficiency of the superficial, deep or perforating venous system, or a combination of these. One of the most severe complications of CVI is atrophie blanche. Other severe complications are leg ulcers and dermato- et liposclerosis. Atrophie blanche needs special attention, since recurrent ulcers is more seen in patients with CVI with atrophie blanche than in patients with CVI without atrophie blanche (Chapter 3). In a group patients which we studied in a phlebological outpatient clinic, atrophie blanche was seen in more than 30 percent of the patients with venous leg ulcers. A possible explanation for this high percentage of atrophie blanche might be that patients with slow healing leg ulcers and therapeutic resistant patients are more likely to visit a specialised outpatient clinic. Of all patients with venous leg ulcers, a certain percentage of these patients will never visit a doctor at all, while another percentage will only visit a family doctor. So this percentage might not be representative for all patients with leg ulcers. It does, however, indicate the importance of atrophie blanche. Studying the percentage of atrophie blanche in patients with leg ulcers visiting a family doctor will (probably) also not be representative, since a certain group of patients with atrophie blanche, will visit a specialised outpatient clinic right away, and certainly if the ulcers are recurrent.
Normally venous leg ulcers are relatively painless. Leg ulcers in atrophie blanche lesions, however, show another behaviour, they can be very painful. This might be another reason while this group of patients will visit a phlebological clinic more often. Another complication of ulcers in atrophie blanche lesions is, that they show a much more slow tendency of wound healing than other venous leg ulcers. These facts together make it important to investigate the pathogenesis of atrophie blanche.
In studying patients with CVI with and without atrophie blanche it is difficult to categorise patients. The classification of Widmer[1] is easy to use in daily practice but is only based on clinical signs. The Hawaii[2] classification is much more complicated, but still not complete because haemodynamic disturbances are not

classified. Therefore the Widmer classification is still used in most studies, in combination with venous refill time.
Basically the same pathogenesis in macrocirculation is seen in all the complications of patients with CVI. A continuous high venous pressure during standing and walking is transmitted retrograde to the microvascular system of the skin. Until now it is unclear which (local) factors cause the different complications of CVI. There are four major theories for developing skin complications and the formation of venous leg ulcers 1) the development of fibrin cuffs around capillaries[3], 2) intracapillary microthrombi[4], 3) white cell trapping[5], and 4) the growth factor trap hypothesis[6]. There are indications that especially in atrophie blanche, microthrombi play a role in pathogenesis.

MICROCIRCULATION

Increased venous pressure in macrocirculation is transmitted retrograde to the microcirculation leading to dilatation and enlargement and formation of glomerulus-like capillaries. The inter endothelial spaces are enlarged and an abnormal capillary filtration rate induces an accumulation of initially water, ions and salts, and later also other larger plasma components in the interstitium. Skin biopsies show furthermore an apparent proliferation of capillaries and a so-called peri-capillary halo. The total number of capillaries is reduced, although in histological sections the tortuous loops might give the impression of a capillary increase. The exact pathophysiologic pathway of the development of CVI, however, is still unsolved.
In studying the microcirculation of CVI skin, several differences between atrophie blanche and mild CVI are seen. Transcutaneous oxygen measurements are decreased extremely in atrophie blanche, sometimes down to zero. This might be caused by the fact that in atrophie blanche lesions avascular fields are seen. Bollinger explained this by the formation of microthrombi, which will result in minor skin infarctions. This theory is supported by studies in which endothelial proliferation and thickened and swollen capillaries and arterioles in histology are seen. Some vessels are occluded with fibrinoid material or erythrocytes. In patients with CVI without atrophie blanche, transcutaneous oxygen measurements are also decreased, but they are not reaching zero. In our study a clear difference in basic transcutaneous oxygen values was seen between atrophie blanche and mild CVI patients. No statistically difference was seen in basic oxygen values between healthy controls and mild CVI patients (chapter 4). A possible explanation for this might be the small group of patients and a large interpatient variation.
A different reaction pattern in transcutaneous oxygen values during artificially induced venous hypertension is seen. In atrophie blanche transcutaneous oxygen measurements show a decrease at 40 mmHg venous hypertension, while in mild CVI a significant decrease is seen at 60 mmHg artificially induced venous hypertension. Healthy controls show a significant decrease in transcutaneous oxygen measurements at 80 mmHg artificially induced venous hypertension (chapter 4). In the literature an increase of transcutaneous oxygen values during

venous hypertension is described in both the skin of healthy controls and CVI patients. In these studies venous hypertension was induced by a sitting position (dependent leg). A possible explanation might be that a sitting position causes an increase in arterial inflow, while a upper thigh cuff might cause a decrease of arterial inflow. The decrease of arterial inflow as result of the upper thigh cuff is, however, probably very small. Sitting position also causes a lesser increase in venous hypertension than a upper thigh cuff of 80 mmHg does. Venous hypertension caused by an upper thigh cuff might be a more realistic reflection of changes in microcirculation in severe CVI than venous hypertension in sitting position does.

In our study (chapter 4) healthy controls show a tendency of increase in transcutaneous oxygen values at 20 and 40 mmHg, but show a significant decrease at 80 mmHg artificially induced venous hypertension. The importance of the differences in decrease at several levels of artificially induced venous hypertension is unclear. An explanation for these different reaction patterns might be that the microcirculation in atrophie blanche is more disturbed than in mild CVI. Less extra venous pressure is necessary to induce a decrease in microcirculatory functions since vascular reserve capacity is all used. It would be interesting to study the reaction of venous hypertension in patients with CVI and dermato- et liposclerosis and to compare that with our study results. Since dermato- et liposclerosis is also a severe complication of CVI, a similar reaction pattern as in patients with atrophie blanche is expected.

We were able to demonstrate differences in basic resting flux, measured with laser Doppler perfusing imager in patients with atrophie blanche. Increased basic resting flux in patients with CVI in general or dermato- et liposclerotic skin was described before. However, no information was known about atrophie blanche. In atrophie blanche lesions, basic flux was increased compared with healthy controls and compared with normal skin in the knee of patients with CVI (chapter 4).

An increased basic resting flux in areas with atrophie blanche lesions can be explained by the morphology of atrophie blanche. Laser Doppler perfusing imager measures 1 to 1.5 mm in depth, where both a part of capillaries is seen and arterioles and small veins. In atrophie blanche lesions the number of capillaries is decreased so the blood volume has to pass through a decreased capacity of capillaries. It is possible that as a result the basic resting flux is increased. Summarised the increased flux could represent an increase in flow in arterioles and small veins, while the number of capillaries is decreased.

A decrease in flux was seen during venous hypertension in atrophie blanche and healthy controls. The venoarteriolar response was similar in both groups. Also a recent study with a double-wavelength laser Doppler probe did not show an impaired venoarteriolar response in the legs of patients with CVI compared with healthy controls.[7] In our study no rebound reaction was seen. This might be explained by a lack of reserve capacity of the microcirculation. However, also healthy controls showed no rebound reaction. It is also possible that a rebound reaction is mainly seen after arterial occlusion.

The contradiction of increased flux and decreased transcutaneous oxygen values in atrophie blanche lesions is hard to explain. Some authors suggest that

arteriovenous anastomosis cause this discrepancy. A possible explanation might also be that transcutaneous oxygen values predominantly reflects the effects caused by the capillaries (comprising a considerable part of the nutritive vessels), which are partly occluded by microthrombi and might be influenced by fibrin cuffs, trapping of leucocytes and oedema whereas the laser Doppler perfusing imager mainly reflects the flux of blood in the deeper skin layers (which mainly serve the thermo-regulation). Chronic venous hypertension may cause a continue increased flux in the deep vessels, and because of dilatation, a decreased flux in the superficial vessels, which increase the risk for developing microthrombi. Decreased transcutaneous oxygen values and decreased number of capillaries in atrophie blanche support this hypothesis.

More details about the microcirculation can be observed with capillary microscopy. With capillary microscopy only the most superficial capillaries can be seen. Because atrophy blanche lesions are atrophic, this skin is easier to study with capillary microscopy than skin of healthy controls.
We were able to demonstrate a decrease in capillary blood cell velocity during different steps of artificially induced venous hypertension in capillaries of CVI skin (chapter 5). There was also an increase in the number of standstills and the total duration of standstill (times x duration) during increasing venous hypertension. No difference was seen in reaction pattern during venous hypertension in patients with CVI with atrophie blanche and without atrophie blanche, although there was a tendency of increased number of standstills in atrophie blanche lesions compared with CVI skin.
The origin, importance and complications of these standstills are unclear. Standstills are probably a normal physiological reaction on venous hypertension, since they are both seen in nailfold capillaries of healthy controls and in the medial ankle region.
Standstills might be a first event for developing microthrombi or standstills might be the result of microthrombi. Both reduction in capillary flow and the number of standstills are likely to play an important role in formation of microthrombi. It is known that endothelium of capillaries in CVI skin are damaged and that leucocytes adhere to the endothelial cells. The nature of active leucocytes adherence is not fully understood, however, adherence proteins (like intercellular adhesion molecule (ICAM-1) and endothelial leucocyte adhesion molecule (ELAM-1)) do play an important role. Veraart *et al.* found a moderate to strong expression of ELAM-1 under leg ulcers, and no up-regulation of ICAM-1 along the border area of a ulcer.[8] Other studies in the expression of ICAM-1 and ELAM-1 in liposclerotic skin and healthy controls skin showed no significant difference. Adherence of the leucocytes may cause partial obstruction of the capillary lumen and reduce bloodflow. In addition patients with CVI show a decreased fibrinolysis. These facts together may cause microthrombi in CVI skin, while in other places, decrease in capillary flow and standstills cause no microthrombi.
The efflorescencies of patients with CVI with or without atrophie blanche and/or with or without dermato- et liposclerosis is extremely different. It is suggested that the clinical signs of CVI are based on the same basic alterations of the skin

microcirculation. Local factors as disturbed fibrinolysis, extravasation of erythrocytes and extra cellular matrix, will be responsible for the difference in skin manifestations in the course of CVI. Atrophie blanche is only a clinical entity correlated to be a more severe stage than CVI without atrophie blanche. It is clear that increased venous walking pressure results into decreased capillary density and dilated, tortuous capillaries with halo formation. A decreased flow in capillaries leads to sludge formation and stasis, resulting together with leucocyte adhesion and local coagulation disorders into intravascular coagulation, decreased $TcPO_2$ and microthrombi.
Further studies are necessary to elucidate the pathogenesis. It would be interesting to study the differences in bloodcell velocity and standstills in capillaries during venous hypertension in the medial ankle region in healthy controls and patients with CVI. Patients with CVI should be categorised in mild CVI, CVI with dermato- et liposclerosis and CVI with atrophie blanche. Studies with capillary microscopy in dermato- et liposclerosis without the use of sodium fluorescence is, however, almost impossible. Also in healthy controls the skin in the medial ankle region only show comma shaped capillaries, in which it seems impossible to measure capillary blood cell velocity. Besides capillary bloodcell velocity and standstills the morphological abnormalities of the capillaries can be studied. This, however, will also be difficult because the different patterns described for capillaries can be applied on nailfold capillaries, but not on capillaries of other parts of the skin. It is also not very likely that the tortuous capillaries will change to normal capillaries. Recently, the effect of compression-therapy on microcirculation was studied with capillarymicroscopy.[9] Capillary density increased during therapy. Capillary density, however, also seems a more appropiate method for mild CVI than CVI with atrophie blanche.

FACTOR V LEIDEN

Both thrombi in micro,- and macrocirculation might play a role in the pathogenesis of CVI. In 30 to 50 percent of patients with CVI and leg ulcers, a history of deep venous thrombosis is seen. Deep venous thrombosis can be caused by several factors. Recently a high prevalence of factor V Leiden mutation in patients with deep venous thrombosis was studied. Heterozygous factor V Leiden mutation increases the risk of venous thrombosis 5-7 fold. Factor V Leiden mutation accounts for 20% of DVT's, and for 50% of familial venous thrombosis.
We studied the prevalence of factor V Leiden mutation in a group of 92 patients with CVI and venous leg ulcers and a control group of 53 patients to investigate whether factor V Leiden mutation is seen more in CVI patients and especially in patients with CVI with atrophie blanche (chapter 6). Factor V Leiden mutation was seen significantly more in patients with CVI and venous leg ulcers than in the control group (23% versus 7.5%).
In the patient group with factor V Leiden mutation a history of deep venous thrombosis and pulmonary embolism was more present. Also recurrent deep venous thrombosis and recurrent leg ulcers of 9 times or more, was seen

significantly more in this group of patients. No difference was seen in venous refill time, or presence of atrophie blanche and/or dermato- et liposclerosis.
Patients with factor V Leiden mutation have an increased risk in developing deep venous thrombosis and recurrent leg ulcers. Since no difference was seen in patient groups with atrophie blanche or dermato- et liposclerosis, a relation between thrombi in macrocirculation and thrombi in microcirculation could not be estimated.
Concerning the results of the studies in atrophie blanche lesions and patients with CVI, as mentioned above, a different reaction pattern in several complications of CVI is sometimes suggested. A closer analysis of the results, however, makes it more likely that complications of CVI are the result of the same mechanism with different stadia. These different stadia, which can change in time, may sometimes suggest different reaction patterns. Further studies are necessary to investigate the effect of compression therapy and anticoagulants in preventing CVI and leg ulcers in patients with deep venous thrombosis.

PILOT STUDY LOW MOLECULAR WEIGHT HEPARIN

In daily practice it would be interesting and of great social economic value how complications of CVI can be prevented. It is well known that compression therapy is a cornerstone in the treatment of CVI. But also in patients with adequate compression therapy, leg ulceration is seen.
A combination of phenformin and ethylestrenol, which enhances endogenous blood fibrinolytic activity by increasing plasminogen activating enzymes, appeared to be effective in treating atrophie blanche ulcers. In 1977 phenformin was removed from the general market by FDA decision because of its side-effects. Since ethylestrenol alone is not effective, other drugs are suggested to use as a substitute. Case reports of effective treatment in venous leg ulcers with low molecular weight heparins suggest an alternative. We studied the influence of low molecular weight heparin (LMWH) in the microcirculation of the skin of patients with atrophie blanche (chapter 7). The influence of 10 weeks with Clivarin was determined with transcutaneous oxygen measurements, laser doppler perfusion imager and capillary microscopy. No improvement in basic transcutaneous oxygen values and flux or in venoarteriolar response could be found. Basic capillary blood cell velocity and the decrease of capillary bloodcell velocity during venous hypertension, did not improve during treatment with Clivarin. A tendency of decrease in number of standstills in capillary flow during venous hypertension was seen after 10 weeks of treatment. This difference was however not significant. It is suggestive however, that treatment with LMWH's might be successful in the additional treatment of leg ulcers, or in prevention of leg ulcers. Maybe the used parameters in measuring improvement of the microcirculation are not sensitive enough, to measure improvements in the microcirculation. Also the period of 10 weeks might be too short to measure improvements in the microcirculation. It can be concluded that further studies are necessary to measure additional effects of drugs to compression therapy to improve complications of CVI. It would then be

interesting not only to study the effect of LMWH's, but also of aspirin and the combination of both. It is possible that the combination of LMWH's and aspirin have a synergetic effect.

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CHAPTER 9

SAMENVATTING

SAMENVATTING

Atrophie blanche is een vaak voorkomende complicatie van patiënten met chronische veneuze insufficiëntie (CVI). In het dagelijks leven kan atrophie blanche pijnlijke, slecht genezende "open benen" veroorzaken, welke van grote invloed zijn op het dagelijks functioneren van de patiënt.
CVI is een complex van symptomen welke veroorzaakt wordt door een continue verhoogde ambulatoire veneuze druk, waarbij een te geringe drukdaling in het veneuze stelsel tijdens het lopen centraal staat. Dit wordt veroorzaakt door insufficiëntie (slecht functionerende kleppen) van het oppervlakkige, perforerende en/of diepe veneuze systeem (door de zogenaamde "oppervlakkige en/of diepe spataders"). Bij iemand met intacte kleppen daalt de druk tijdens het lopen en bewegen van de kuit- en voetspieren; bij defecte kleppen gebeurt dit niet en ontstaan er bij spiercontracties drukgolven de verkeerde kant op, richting de kleine bloedvaatjes (capillairen) in de huid. De meest voorkomende oorzaak voor deze klepinsufficiëntie zijn primaire varices (spataders) of een klepbeschadiging van de diep gelegen venen na een doorgemaakt trombose been.
Naast uiting van CVI wordt atrophie blanche ook gezien in patiënten met interne afwijkingen. Klinisch kan tussen deze twee vormen van atrophie blanche geen onderscheid gemaakt worden, behoudens dat atrophie blanche als uiting van CVI altijd op het onderbeen gezien wordt, terwijl atrophie blanche bij interne afwijkingen overal op het lichaam kan voor komen.

In **hoofdstuk 1** wordt een overzicht gegeven over CVI en diep veneuze trombose. In het bijzonder wordt de pathofysiologie, de microcirculatie en de behandeling van CVI besproken en de relatie van diep veneuze trombose, stollings afwijkingen en CVI.
Het doel van diverse onderzoeken wordt beschreven. Allereerst wilden we een juist overzicht krijgen van de prevalentie van atrophie blanche in veneuze ulcera ("open benen"), en of de ulcera in atrophie blanche een grotere neiging hebben tot recidiveren. Daarnaast wilden we een compleet overzicht krijgen van wat er tot op dit moment bekend is van atrophie blanche.
Een ander doel was het verkrijgen van inzicht in het effect van artificieel geïnduceerde veneuze hypertensie op de microcirculatie in atrophie blanche met behulp van laser Doppler imaging, transcutane zuurstofmeting en de capillair microscoop. We waren geïnteresseerd of er een verschillend reactie patroon bij veneuze druk optreedt bij patiënten met atrophie blanche, patiënten met CVI zonder atrophie blanche en gezonde controles.
Daarnaast waren we geïnteresseerd of bij patiënt en met veneuze ulcera en atrophie blanche factor V Leiden vaker voor komt dan bij patiënten met veneuze ulcera zonder atrophie blanche en of er een verschil in prevalentie is ten opzichte van gezonde controles.
We vroegen ons af of het voorschrijven van laag moleculair heparine zinvol is in de behandeling of preventie van veneuze ulcera in atrophie blanche. Hiervoor werd de invloed van laag moleculair heparine op de microcirculatie van atrophie blanche bestudeerd.

In **hoofdstuk 2** wordt een algemeen overzicht gegeven over atrophie blanche. Atrophie blanche wordt beschreven in diverse ziektebeelden, maar wordt eigenlijk alleen regelmatig gezien in scleroderma en systemische lupus erythematodes. Het meest frequent wordt atrophie blanche echter gezien als onderdeel van CVI. Het is niet altijd eenvoudig om de juiste informatie over atrophie blanche te vinden omdat diverse synoniemen gebruikt worden (meer dan 7). De naam atrophie blanche verdient de voorkeur boven het meest gebruikte synoniem livedo vasculitis.
Bijzondere aandacht wordt gegeven aan de pathogenese van atrophie blanche. Tot nu toe is het onduidelijk welke factoren het meest belangrijk zijn in de pathogenese van CVI en in het bijzonder van atrophie blanche. De belangrijkste theorie voor de pathogenese van atrophie blanche lijkt de theorie van de microthrombi. Volgens deze theorie vormen zich stolsels in de meest kleine vaatjes van de huid (de capillairen), zodat als het ware kleine infarcten van de huid optreden. Omdat in atrophie blanche grote delen zonder bloedvaatjes worden gezien, en omdat onder de microscoop verstoppingen van diverse capillairen wordt gezien lijkt deze theorie van toepassing op atrophie blanche.
Tevens wordt een overzicht gegeven van diverse behandelingen van atrophie blanche. Meeste behandelingen die in de literatuur beschreven worden, zijn echter geen goed beschreven studies, maar individuele case reports, waarin hoogstens 2 of 3 patiënten beschreven worden.

In **hoofdstuk 3** wordt de prevalentie van atrophie blanche in patiënten met veneuze ulcera bestudeerd. In een grote groep patiënten met veneuze ulcera werd atrophie blanche gezien in 31% van de manlijke patiënten en in 44% van de vrouwelijke patiënten. Deze getallen zijn hoger dan in de literatuur wordt beschreven. Dit kan veroorzaakt worden doordat voornamelijk patiënten met een therapie resistent ulcus een polikliniek bezoeken die gespecialiseerd is in de flebologie. Bij patiënten met atrophie blanche werden significant meer recidiverende ulcera gezien (71%) dan bij patiënten met CVI zonder atrophie blanche. Dit onderschrijft het belang van het goed herkennen van atrophie blanche en het belang van een goede en adequate behandeling.

In **hoofdstuk 4** worden de resultaten gepresenteerd van een studie waarin de verandering in de microcirculatie van de huid tijdens artificieel geïnduceerde veneuze hypertensie geobjectiveerd wordt met behulp van transcutane zuurstofwaarden en laser doppler perfusion imager metingen in patiënten met CVI met en zonder atrophie blanche. Het is algemeen bekend dat in atrophie blanche de transcutane zuurstofwaarden extreem laag zijn, bijna nul. Een verschillend reactiepatroon op veneuze hypertensie werd gezien in de drie bestudeerde groepen. In atrophie blanche werd een daling in transcutane zuurstof waarden gezien bij 40 mmHg, in CVI huid zonder atrophie blanche bij 60 mmHg en in gezonde controles bij 80 mmHg artificieel geïnduceerde veneuze hypertensie.
Flux in de huid werd gemeten met de laser Doppler perfusion imager. Flux in patiënten met atrophie blanche was significant hoger dan in CVI huid zonder

atrophie blanche en gezonde controles. Een daling in de flux trad op bij artificieel geïnduceerde veneuze hypertensie. Deze daling was vergelijkbaar in patiënten met atrophie blanche en gezonde controles, dat wil zeggen, de venoarteriolaire reactie was gelijk in alle bestudeerde groepen. Geen rebound fenomeen werd gezien, wat een tekort aan reserve capaciteit van de microcirculatie veronderstelt.

In **hoofdstuk 5** worden de resultaten besproken van de studie, waarin het effect van veneuze hypertensie op de microcirculatie van de huid gemeten wordt met behulp van een capillair microscoop. De capillair microscoop is in het bijzonder geschikt voor metingen in atrophie blanche gebied, omdat de huid daar erg dun is, en zo de capillairen makkelijk zichtbaar zijn. Het is bekend dat de capillairen in dit gebied vergroot zijn en een glomerulus-achtig aspect vertonen. Twee groepen patiënten werden bestudeerd, patiënten met CVI zonder en met atrophie blanche. Tijdens diverse artificieel geïnduceerde veneuze drukstappen daalde de capillaire bloedsnelheid en nam het aantal flow stops en de totale duur van flow stop (aantal x duur stops) in de capillairen toe. Bij 20 mmHg vertoonden beide groepen een significante toename in stops. Bij hogere veneuze drukken nam het aantal flow-stops toe, maar alleen bij patiënten met atrophie blanche werd nog een significante stijging in het aantal flow-stops gezien bij stijging van 20 naar 40 mmHg. In het algemeen kan gesteld worden dat flow-stops in capillairen ten gevolge van artificieel geïnduceerde veneuze hypertensie een normaal fysiologisch verschijnsel zijn, daar ze zowel voorkomen bij patiënten met atrophie blanche als bij gezonde controles. Bij atrophie blanche speelt zowel een daling in capillaire bloedsnelheid, als een toename in capillaire flow-stops en totale duur van flow stops mogelijk een rol in de vorming van microthrombi. Bij chronische verhoogde veneuze druk is er namelijk ook nog sprake van schade aan het endotheel van de capillairen, leidend tot een verminderde fibrinolytische functie. Deze processen, samen met het verstrikt raken van leucocyten in de capillairen, stimuleren waarschijnlijk de vorming van microthrombi.

Hoofdstuk 6 behandelt de resultaten van een studie waarin de prevalentie van factor V Leiden mutatie in patiënten met veneuze ulcera bestudeerd wordt. Sinds een aantal jaren is het bekend dat bij een grote groep patiënten met een trombose been, factor V Leiden mutatie gezien wordt. Factor V Leiden mutatie is een afwijking op een gen waardoor het bloed als het ware sneller stolt. Het is bekend dat bij bijna de helft van de patiënten met veneuze ulcera vermoed wordt dat ze in het verleden een trombose been hebben doorgemaakt. Bij 92 patiënten met veneuze ulcera, werd factor V Leiden mutatie gezien in 23%. In een gezonde controle groep werd slechts in 7.5% factor V Leiden mutatie gezien. Er werd geen relatie gezien tussen factor V Leiden en atrophie blanche. Wel was er een duidelijke, significante relatie tussen veelvuldig recidiverende ulcera (9 keer of meer) en factor V Leiden mutatie. Er wordt door ons verondersteld dat factor V Leiden mutatie een verhoogd risico vormt voor het ontwikkelen van ernstige en recidiverende veneuze ulcera. Meer studies zijn nodig om het effect van de gecombineerde behandeling van compressie therapie en anticoagulantia op de

preventie van CVI en veneuze ulcera bij patiënten met een doorgemaakt trombose been te bestuderen.

In **hoofdstuk 7** worden de resultaten gegeven van de studie waarin het effect van laag moleculaire heparine op de microcirculatie van de huid in patiënten met atrophie blanche bestudeerd wordt. Tien patiënten met atrophie blanche werden gedurende 10 weken behandeld met het laag moleculaire heparine, Clivarine. Aan het begin en aan het einde van de studie werden metingen van de microcirculatie van de huid verricht met behulp van transcutane zuurstofwaarden, laser Doppler metingen en de capillair microscoop. Niet alleen de uitgangswaarden werden vergeleken, maar ook of het effect op artificieel geïnduceerde veneuze hypertensie gedurende deze 10 weken verbeterde. Er werd na tien weken behandelen geen verbetering gemeten in de uitgangswaarden. Wel was er een duidelijke tendens in afname van het aantal capillaire flow-stops tijdens veneuze hypertensie. Deze afname was echter niet statistisch significant.

Hoofdstuk 8 vormt een algemene discussie, waarin de gegevens van de studies van de voorafgaande hoofdstukken besproken worden. Atrophie blanche vormt een ernstige complicatie van CVI, met een prevalentie van 30% . In patiënten met CVI en atrophie blanche worden recidiverende ulcera meer gezien dan in patiënten met CVI zonder atrophie blanche.
In de microcirculatie van de atrophie blanche huid worden diverse afwijkingen gezien. Transcutane zuurstofwaarden zijn in dit gebied extreem laag, en dalen tijdens "veneuze hypertensie stappen" eerder dan in CVI huid zonder atrophie blanche. Dit veronderstelt een tekort aan reserve capaciteit in de microcirculatie van atrophie blanche. De flux in atrophie blanche is verhoogd, vergeleken met CVI huid zonder atrophie blanche en gezonde controles. De venoarteriolaire reactie van beiden groepen is gelijk. Veneuze hypertensie veroorzaakt een daling in capillaire bloed snelheid en een toename in het aantal capillaire flow stops en totale duur van flow-stop in atrophie blanche. Deze resultaten ondersteunen de theorie van de microthrombi.
Geen relatie werd gezien tussen atrophie blanche en factor V Leiden mutatie. Recidiverende veneuze ulcera worden echter wel significant meer gezien in patiënten met factor V Leiden mutatie, wat een ernstiger complicatie in het post thrombotisch syndroom veronderstelt. Factor V Leiden mutatie wordt significant meer gezien in patiënten met veneuze ulcera vergeleken met gezonde controles.
Behandeling met laag moleculair heparine's gedurende 10 weken resulteert niet in objectiveerbare verbetering in de microcirculatie van de atrophie blanche huid, alhoewel wel een duidelijke afname van het aantal capillaire stops tijdens veneuze hypertensie wordt gezien. Meer studies zijn nodig om het effect van behandeling in de preventie van atrophie blanche te bestuderen. Het zou interessant zijn of een gecombineerde behandeling van laag moleculaire heparine en aspirine wel tot objectiveerbare verbeteringen zou leiden, daar deze twee mogelijk een synergistisch effect hebben.

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Curriculum Vitae

Birgitte Maessen-Visch werd op 28 november 1964 geboren te Nijmegen. Zij behaalde haar eindexamen VWO in 1983 aan het Willem de Zwijger College te Bussum. Na een jaar Highschool in Morris USA, en een jaar Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen, waarvoor zij haar propaedeuse behaalde, startte ze in 1985 de studie Geneeskunde aan de Katholieke Universiteit Nijmegen. Zij behaalde in 1991 haar artsexamen. Van 1991 tot 1992 was zij werkzaam als AGNIO op de afdeling dermatologie van het Clara ziekenhuis te Rotterdam onder leiding van mevrouw van Hussen-Brok, en van 1992 tot 1994 op de afdeling dermatologie van het Sint Joseph Ziekenhuis te Veghel/Uden onder leiding van de heren Groeneweg en Bruins. In deze periode begon zij met wetenschappelijk onderzoek. Op 1 maart 1994 werd de opleiding dermatologie onder leiding van prof. H.A.M. Neumann in het academisch ziekenhuis Maastricht gestart. Na haar registratie als dermatoloog op 1 maart 1998 is zij werkzaam als part-time staflid aan de vakgroep dermatologie in het academisch ziekenhuis Maastricht en neemt zij waar bij dr. R. Korstanje te Geldrop.
Zij is sinds 1992 getrouwd met Michel Maessen en ze hebben samen een dochter, Niki.

LIST OF ABBREVIATIONS

AB	atrophie blanche
BRF	basic resting flux
CVI	chronic venous insufficiency
DVT	deep venous thrombosis
ELAM	endothelial leucocyte adhesion molecule
ICAM	intercellular adhesion molecule
LDF	laser Doppler fluxmetry
LDPI	laser Doppler perfusion imager
PAI	plasminogen activator inhibitor
$TcPO_2$	transcutaneous oxygen pressure
t-PA	tissue plasminogen activator
SLE	systemic lupus erythematodus
VAR	venoarteriolar response
VOC	venous occlusion