Pathophysiological mechanisms of chronic venous disease and their role in C0s clinical class

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Abstract:
The aim of this review is to provide a clear understanding of the pathophysiological mechanisms of chronic venous disease (CVD) at different clinical stages and the possible role of these mechanisms in the development of symptoms in C0s clinical class of the Clinical, Etiologic, Anatomic, and Pathophysiologic classification, which consists of symptomatic patients without any visible or palpable signs of venous disease. The prevalence of C0s class in several epidemiological studies varies between 13% and 23% of the general population. Wall remodeling and valve destruction due to white cell endothelial interaction is the main cause of primary varicose veins, while deep vein thrombosis produces secondary changes leading to the postthrombotic syndrome. The underlying mechanism of the skin changes and ulceration is venous hypertension, which is transmitted to the skin microcirculation. Over the last 10 years, an improved videocapillaroscopic technique, the orthogonal polarization spectral imaging technique demonstrated that quantitative measurements in the skin microcirculation are progressively altered from C0 to C5 patients and that values in CVD patients are significantly different from healthy individuals (P < 0.05): capillary diameter increases and capillary morphology worsens from C2 to C5; diameter of the dermal papilla and diameter of the capillary bulk increase from C3 to C5; and functional capillary density (FCD) decreases from C4 to C5. In addition, significant changes have been shown between C0a and C0s patients despite the presence of normal conventional duplex scans in the latter: a decrease of FCD and an increase in the diameter of the dermal papilla. Functional abnormalities found to be present in C0s patients by recent studies include increased compliance of the venous wall (hypotonic phlebopathy), dilatation of deep veins in the calf producing an abnormally increased venous volume, reduction in emptying of venous reservoir, reduction in the vеноarteriolar response on standing, and blood reflux in small venules despite a normal conventional duplex scan. However, most of the studies are small, and their findings need to be confirmed by larger series. It remains to be seen whether functional changes and microcirculatory changes respond to venoactive medications in parallel to the relief of symptoms.

Keywords:
Chronic venous disease, microcirculation, venous wall remodeling

Introduction

Chronic venous disease (CVD) presents with a variable combination of symptoms and signs and is associated with complicated venous hemodynamics that are difficult to understand unless one is familiar with the theory of hemodynamics in collapsible tubes. In addition, it is a progressive condition.

Epidemiological studies have demonstrated that the prevalence of CVD varies between 25% and 85% depending on severity considered and age group[1] with telangiectasias and reticular veins being the most common (80% in men and 85% in women). Varicose
veins (VVVs) are present in 25%–33% of female and 10%–40% of male adults. The prevalence of edema and skin changes due to CVD such as hyperpigmentation and eczema varies from 3% to 11% of the population. Venous ulcers occur in about 0.3% of the adult population in Western countries[1].

Symptoms[2] and signs[3] related to CVD are shown in Table 1. Symptoms describe what the patient feels. Signs are elicited by the doctor and are typically used to define the clinical classes of the Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classification. However, what the patient seeks is relief of symptoms, often more than improved appearance. What the doctor aims for is not only to relieve symptoms and improve appearance but also to stop disease progression.

One of the diagnostic problems is that symptoms are not specific for CVD and there is a poor correlation between symptoms and signs. Another problem is that symptoms of CVD are often present without any evidence of an abnormality on clinical examination or routine duplex scanning (C0s CEAP clinical class).

The aim of this review is to provide a clear understanding of the pathophysiological mechanisms of CVD at different clinical stages and the possible role of these mechanisms in the development of symptoms in C0s clinical class.

Primary chronic venous disease
Primary varicose veins are very common in the adult population and are frequently responsible for skin changes as well as 40% of venous leg ulcers despite the presence of normal deep veins.[1] In recent years, the role of leukocyte–endothelium interaction as a key factor in the initiation of primary CVD has become better understood. This process starts with leukocyte adhesion, degranulation, and migration under the endothelium producing chronic inflammation with eventual remodeling of venous wall and valves.[4] The resulting damage produces valve cusp distortion, reflux, and venous hypertension.[5]

During standing, venous pressure in the veins of the foot and ankle is approximately 90 mmHg depending on the height of the individual. This is the hydrostatic pressure from the level of the heart to the foot. During walking in a normal person with competent venous valves and a healthy calf muscle pump, the pressure decreases to 25 mmHg. In the presence of damaged valves, what determines venous pressure during walking (ambulatory venous pressure) is the volume of blood refluxing (ml/sec) during the period of 1.0–1.5 s when the foot is off the ground, before the onset of the next step and muscular contraction. A steady state is reached after the first ten steps when the amount of blood refluxing during muscle relaxation equals the amount expelled during muscle contraction. A high rate of reflux is associated with rapid filling of the veins before the next muscle contraction ensues and results in rapid elevation of pressure and a high mean venous pressure during walking. A low rate of reflux is associated with a slow filling of the veins before the next muscle contraction ensues and results in a slow elevation of pressure and a low mean venous pressure during walking. The rate of reflux, AVP, and duration of standing or sitting periods determine the mean venous pressure throughout the day and the prevalence of skin changes and ulceration.[5]

Secondary chronic venous disease
The postthrombotic syndrome is responsible for edema, skin changes, and 60% of venous ulcers and also for the development of secondary varicose veins acting as collateral vessels. Persistent obstruction due to failed recanalization and recurrence of deep vein thrombosis or reflux due to damage of the deep venous valves also result in venous hypertension. The combination of both reflux and obstruction of the deep veins is responsible for the most severe symptoms and signs. In cases of severe outflow obstruction, venous pressure during walking may increase to levels above 90 mmHg.

Mechanical dysfunction of the calf muscle pump may enhance the development of leg ulceration emphasizing the importance of the range of ankle motion[8] and patient activity.[7]

Incompetent Perforating Veins
Incompetent perforating veins (IPVs) can be defined as those that penetrate the deep fascia and permit flow

### Table 1: Symptoms, signs, and CEAP clinical class

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CEAP Clinical Class</th>
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<tbody>
<tr>
<td>Heaviness</td>
<td>C0: Absence of visible or palpable signs</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Sensation of swelling</td>
<td>C0: Normal, asymptomatic subjects</td>
</tr>
<tr>
<td>Restless legs</td>
<td>C0: Symptomatic</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>C1: Telangiectasias, reticular veins</td>
</tr>
<tr>
<td>Night time cramps</td>
<td>C2: Varicose veins</td>
</tr>
<tr>
<td>Tiredness</td>
<td>C3: Oedema</td>
</tr>
<tr>
<td>Throbbing</td>
<td>C4: Skin changes</td>
</tr>
<tr>
<td>Itching</td>
<td>C5: Healed venous ulcer</td>
</tr>
<tr>
<td>Signs and CEAP clinical class</td>
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<tr>
<td>C0: Normal, asymptomatic subjects</td>
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<tr>
<td>C3: Oedema</td>
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<tr>
<td>C4: Skin changes</td>
<td></td>
</tr>
<tr>
<td>Pigmentation, Eczema</td>
<td></td>
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<tr>
<td>Lipodermatosclerosis, atrophie blanche</td>
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from the deep to the superficial veins. The flow of calf
IPVs is often bidirectional, outward during muscular
contraction, and inward during relaxation. In normal
legs and in the majority of patients with primary
uncomplicated varicose veins, the net flow is inward from
the superficial to the deep veins (reentry perforators),
as first demonstrated in 1891 by Trendelenburg[8] and
more recently by Bjordal who used electromagnetic
flow meters during exercise.[9] The inward net flow
during exercise is the basis of the Perthes test. The net
flow in IPVs of the calf is also inward even in patients
with femoral vein reflux, provided the popliteal valves
are competent. However, in the presence of popliteal
valve incompetence (axial reflux), and especially when
there is associated deep vein obstruction, the flow is
predominantly outward.[9,10]

IPVs are associated with superficial and/or deep-vein
reflux but are rarely found in the absence of reflux.[11-13]
The prevalence, diameter, volume flow, and velocity of
IPVs increase with clinical severity of CVD irrespective
of presence or absence of coexisting deep venous
incompetence.[9,14-19]

Up to 10% of patients, often women, presenting with
CEAP clinical Class 1–3, have nonsaphenous superficial
reflux in association with unusually located IPVs.[20]

Changes in the Microcirculation

Venous hypertension is transmitted backward to the
microcirculation increasing the hydrostatic pressure in
capillaries. This results in transcapillary filtration that
exceeds lymphatic drainage and thus contributes to
interstitial edema formation. Venous hypertension slows
blood flow in capillaries prompting leukocyte adhesion
to capillary endothelium and initiating an inflammatory
reaction.[21]

In patients with venous hypertension, capillaries
become markedly dilated, elongated, and tortuous,
especially at skin sites with hyperpigmentation and
lipodermatosclerosis (LDS). These changes are associated
with a high overall microvascular blood flow in the
dermis[22] and a decreased flow in nutritional capillaries
with decreased oxygen delivery.[23]

Laser Doppler studies show that in addition to increased
blood flow (red cell flux) in the dermis, there is loss of the
rhythmic vasomotor activity seen in normal skin
and abolition of the venoarteriolar reflex (VAR). The
VAR is an axon reflex elicited by any postural change
that increases venous pressure by 40 mmHg or more. In
normal limbs, the ensuing arteriolar vasodilation and
reduction in skin blood flow is a protective mechanism
in the sitting or standing position.[24]

Over the last 10 years, an improved videocapillaroscopic
technique, the orthogonal polarization spectral imaging
technique used in the Cytoscan (Lekam Medical
Ltd, UK) with sidestream dark field has become
available. Combined with the MicroScan Video
Microscope (MicroVision Medical, The Netherlands)
and lately the Cytocam (Braedius Medical Ltd, The
Netherlands), it has allowed alterations of skin
capillaries to be studied in patients assigned C1 to C6
of the CEAP classification. The Cytoscan has a small
handheld probe which can be noninvasively applied
to the skin to evaluate microcirculatory parameters
such as functional capillary density (FCD), number
of capillaries with flowing red blood cells per unit of
tissue area, representing tissue perfusion evaluated
by capillaries per mm², diameter of dermal papilla
(DDP, μm) to quantify edema, the largest diameter of the
capillary bulk (DCB, μm) to assess its degree of change,
capillary limb diameter (CD, μm) to describe diameter
changes, and capillary morphology (CM, percentage of
abnormal capillaries per field). It has been demonstrated
that all these values are progressively altered from
C1 to C6 patients and that values in CVD patients are
significantly different from healthy subjects (P < 0.05):
capillary diameter increases and CM worsens from C2
to C5; diameter of the dermal papilla and diameter of
the capillary bulk increases from C3 to C5, and FCD
decreases from C4 to C5.[25] In a most recent study,
sicant changes have been shown between (C0a)
asymptomatic normal persons and C0s patients despite
the presence of normal conventional duplex scans.[26]
Using the Cytocam, it was possible to observe changes
in CM: a decrease of FCD and an increase in the diameter
of the dermal papilla.

Alteration of Lymphatic Vessels

Spontaneous contractility of lymphatic vessels contributes
to lymph transport. Internal extensions of
lymphatic endothelial cells act as valves and guarantee
a one-way lymph flow.[27] In a steady state, extravasation
of fluids and proteins from blood vessels is balanced by
lymphatic drainage and return into the bloodstream. If
microvascular filtration in blood capillaries and venules
as occurs in advanced CVD exceeds the capacity for
lymphatic drainage for sufficiently long periods, edema
develops in afflicted areas by accumulation of tissue fluid.

Vascular Biology and Pathophysiology of the
Venous Wall

Varicose veins have different elastic properties from normal
veins. The ratio of Collagen I to Collagen III is altered and
so do dermal fibroblasts from the same patients, suggesting
a systemic disorder with a genetic basis.[28]
Leukocyte activation, adhesion, and migration through the endothelium as a result of altered shear stress\(^{29-31}\) contribute to the inflammation and subsequent remodeling of the venous wall and valves.\(^{4,32-34}\)

Reduction in shear stress also stimulates production of tumor growth factor-β1 by activated endothelial cells and smooth muscle cells (SMCs) inducing SMC migration into the intima and subsequent proliferation. Fibroblasts proliferate and synthesize matrix metalloproteinases (MMPs) overcoming the effect of tissue inhibitors of metalloproteinases (TIMPs). The MMP/TIMP imbalance results in degradation of elastin and collagen.\(^{22,30,35}\) This may contribute to the development of hypertrophic and atrophic venous segments and valve destruction seen in varicose veins. Remodeling of the venous wall and abnormal venous distension prevents valve leaflets from closing properly resulting in reflux.

**Compensatory Mechanisms**

It should be emphasized that the effects of venous hypertension are modified by three compensatory mechanisms. The first mechanism is the ability of the lymphatic system to compensate for the increased lymph that is produced. In some patients, the lymphatic drainage can increase up to ten times and the leg may look normal despite severe hypertension, while in some others, only two times, when overt skin changes occur for the same severity of venous hypertension.\(^{36}\) The second mechanism is the fibrinolytic activity in the blood and tissues that can remove excess extracellular protein and particularly fibrin, which varies from person to person. Skin changes are rare in the presence of AVP <35, and skin changes and ulceration are frequent in the presence of AVP >65. Fibrinolytic activity was measured in a series of 37 patients with moderate venous hypertension with AVP in the range of 35–65. Euglobulin lysis time (ELT) was normal (<240 min) in 12 patients of whom only two had LDS but no ulceration, in contrast to the remaining ten patients with low fibrinolytic activity (ELT >240 min) of whom nine had LDS and seven had both LDS and ulceration (\(P < 0.001\)).\(^{37}\) The third factor is time which exerts an adverse effect on the microcirculation with progressive deterioration.\(^{38}\)

**Pathophysiology of Symptoms**

Pain which is a vague and unpleasant feeling is the result of increase in venous pressure that is transmitted to the microcirculation resulting in activation of sensory multimodal nociceptors of myelinated Aδ and unmyelinated C fibers\(^{39,40}\) through local inflammatory mediators. Throbbing occurs more often in patients with varicose veins and this observation is indicative of a hemodynamic mechanism. Tightness is common in patients with iliacaval obstruction and is thought to be related to fluid accumulation and increased pressure in the anatomical compartments. Venous claudication is the result of severe venous outflow obstruction when the arterial inflow exceeds the venous outflow. In these patients, the recovery time when they stop walking is long, often more than 15 min.\(^{22}\) Heaviness and feeling of swelling are often related to edema but can be present in the absence of edema. It is thought that they are produced by microedema at the microcirculation since they are relieved by venoactive drugs without any actual reduction in leg volume.\(^{22}\) Itching is often associated with skin changes, but it can be an isolated symptom. Inflammation, cytokine, and MMP activation have all been implicated in the pathophysiology.\(^{22}\) The exact causation of cramps, restless legs, tingling, and burning is not clear.

**Pathophysiology of C0s**

C0s Class of the CEAP classification consists of symptomatic patients without any visible or palpable signs of venous disease.\(^{33}\) Recent epidemiological studies have demonstrated that C0s patients are common in the general population. C0s prevalence was 13%–23% in a Polish Study,\(^{41}\) 15% in the San Diego Vein Study,\(^{42}\) 19.7% in the worldwide Vein Consult Program,\(^{43}\) and 14% in the Belgium and Luxemburg Study.\(^{44}\)

The presence of CVD symptoms in the absence of any visible or palpable signs has been described well before the development of the CEAP classification. Such patients have been considered to have functional phlebopathy\(^{45}\) or more recently as functional CVD.\(^{46}\) They were studied in depth with photoplethysmography (PPG), strain gauge plethysmography (SGP), and laser Doppler as well as CW Doppler and Duplex scanning in the Acireale epidemiological study which involved 1031 individuals (age: 30–59).\(^{47}\) In this study, symptoms of CVD were present in 561 (54%). Of these, 325 (58%), i.e., 31% of the whole population studied did not have any visible or palpable varicose veins (C0s). However, 163 (50%) of these had reflux in some veins (femoral, great saphenous vein (GSV) above and below the knee, popliteal, small saphenous vein, and tibial veins). The remaining 164 (15.9% of all the population) did not have any reflux on routine conventional duplex scanning. They were considered to have hypotonic phlebopathy (HP) on the basis of the findings summarized below.

In patients with HP, the mean (±standard deviation) PPG change in voltage from baseline (ΔR) after 10 plantar flexion movements were lower (200 ± 15 V) compared with normal controls (275 ± 40 V) (\(P < 0.005\)) indicating reduced emptying of the venous reservoir. The mean
refilling time was also lower (27 ± 5 s) compared with normal controls (35 ± 10 s) (P < 0.005) indicating a relatively fuller reservoir or some reflux in small venules not examined by ultrasound. However, it was not as low as in patients with varicose veins (10 ± 6 s).

SGP demonstrated that the mean maximum incremental venous volume during venous occlusion was higher (4.5 ± 0.4 ml%) in patients with HP than normal controls (2.9 ± 0.3 ml%) (P < 0.005) indicating increased venous compliance. The decrease in volume (∆V) in the sitting position after 10 plantar flexion/dorsiflexion movements was 2.7 ± 0.5 ml% compared with 1.5 ± 0.4 ml% in the normal controls (P < 0.005) confirming a larger volume in the calf reservoir.

In a subgroup of 20 patients with HP, duplex scanning demonstrated that the increase in vein diameters of the popliteal, tibioperoneal trunk, and gastrocnemial veins on standing were 2–3 times greater than in 10 normal controls.

In a subgroup of 10 patients with HP, laser Doppler showed an increase in standing and resting flux indicating increased cutaneous blood flow. In HP patients, resting flux decreased from 10.4 ± 1.9 in the supine position to 7.28 ± 1.2 in the standing position (only 30% reduction) indicating impaired VAR. In contrast, in 10 normal controls, resting flux decreased from 8.0 ± 0.9 in the supine position to 3.6 ± 0.6 in the standing position indicating normal VAR (>50% reduction) (P < 0.001).

In a recent study, 16 COa normal asymptomatic individuals were compared with 16 COs patients.* In COa patients, resting flux decreased from 10.4 ± 1.9 in the supine position to 7.28 ± 1.2 in the standing position (only 30% reduction) indicating impaired VAR. In contrast, in 10 normal controls, resting flux decreased from 8.0 ± 0.9 in the supine position to 3.6 ± 0.6 in the standing position indicating normal VAR (>50% reduction) (P < 0.001).

Using a different approach, Tsoukanov et al., investigated 41 COs women with duplex scanning in the morning (before 10 am) and in the afternoon (after 6 pm).* Fifteen of these patients did not have any reflux at any time. The remaining 26 patients had reflux in the GSV in the evening but not in the morning (situational reflux). Two patients had axial reflux and 24 had segmental reflux. The evening diameter of the GSV was larger in those with reflux in the evening (P < 0.05). The difference in the GSV between the evening and morning was also greater in the patients with evening reflux than those without any reflux. After 2 months of Micronized purified flavonoid fraction (MPFF) treatment, 22 patients no longer had reflux in the evening, the GSV diameter decreased and so did the difference in diameter between the morning and evening (P < 0.0001). There was a parallel significant decrease in the intensity of symptoms as demonstrated by the VAS score and a significant improvement in quality of life (P < 0.00001).

In a subsequent study by Tsoukanov and Tsukanov involving 294 patients, the prevalence of situational reflux in the GSV was investigated. It was detected in 21 (38.2%) of 55 patients classified as COs, 25 (49.0%) of 51 classified as C1s, and in 32 (17.0%) of 188 classified as C2. After treatment with MPFF 1000 mg for 90 days, in the 46 women with transient reflux in classes COs and C1s, reflux disappeared in 76.1% and there was a significant decrease in the GSV diameters. The intensity of symptoms decreased from 5.2 to 1.7 (P < 0.001) according to the 0–10 visual analog scale. The global index score (CIVIQ-20) decreased from 47.2 ± 7.9 to 28.8 ± 9.1 (P < 0.001).

It appears from several studies summarized above that a significant number of patients in COs clinical class who do not have any reflux or obstruction on routine duplex examination are found to have abnormal venous function such as increased venous compliance and venous volume, reduced emptying of venous reservoir on calf muscle contraction, decreased VAR, evening venous reflux in the main venous trunks, reflux in small venules not normally examined by duplex, and even anatomic changes in the skin dermal papillae. However, the number of patients in most studies is small and the findings need to be confirmed in larger studies. In addition, the future studies should determine the prevalence of these functional abnormalities, their coexistence and which are the most predominant in COa patients and also the contribution of these abnormalities to individual symptoms, disease progression, and response to venoactive drugs or compression. Knowledge of the above should help one provide a rational plan for investigation and management of COs patients.

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Conflicts of interest
There are no conflicts of interest.

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