Endothelial dysfunction
Chronic venous disease

Roman Gardlík, MD, PhD
Institute of Pathophysiology
Institute of Molecular Biomedicine
romangardlik@gmail.com
www.imbm.sk
Endothelium

• A type of epithelium that lines the interior surface of blood vessels and lymphatic vessels
• Single layer of squamous endothelial cells with tight junctions
Figure 1. Endothelium and permeability.

A  Capillary

Continuous Non-fenestrated

Continuous fenestrated

Discontinuous/ sinusoidal

B  Post-capillary venule

Inflammation

William C. Aird Circ Res. 2007;100:158-173
Endothelial cell

- Large amounts of vesicles and caveolae along the luminal surface - transendothelial transport of biologically active substances

FIGURE 1 | The formation of vesicles (50–90 nm in diameter) and caveolae along the luminal surface of endothelial cells (A–C). In the cytoplasm, vesicles often aggregate and fuse, forming vesicular structures of larger sizes (A,B). Some plasmalemmal vesicles can fuse with cell membrane in the area of EC intercellular contacts (C). Transmission electron microscopy (TEM). Scale bars = 100 nm (A–C). Images are adapted from Bobryshev (1983).
Endothelium

- **Mesodermal** origin
- EC are aligned and elongated in direction of flow
- EC line the *entire circulatory system* – one of the largest organ systems
- Unique functions
Endothelium

- Fluid filtration (glomeruli)
- Barrier function
- Blood vessel tone (vasodilation and vasoconstriction)
- **Hemostasis**
- Hormone trafficking
- Inflammation - neutrophil recruitment
- Angiogenesis
- Secretion of mediators – normal vascular function
Barrier function

FIGURE 4 | Scheme of a protein structure of endothelial intercellular junctions (EIJs).
Figure 2. Endothelium and leukocyte trafficking.

William C. Aird Circ Res. 2007;100:158-173
FIGURE 3 | Penetration of a blood cell through the endothelium into the arterial intima. Scanning electron microscopy (SEM). Scale bar = 5 µm. Image is adapted from Bobryshev (1983).
Figure 4. Mechanisms of EC heterogeneity.

A
Differentiation

Endothelial progenitor cell
Artery

Venin
Hematopoietic stem cell

Capillary

Brain
Heart
Kidney

Time

Microenvironment
-/+ 
-/+ 
++ 
++++

Epigenetics
++++ 
+++ 
++ 
+

B
Microenvironment

Protein
Post-translational modification
Transcription factor

C
Epigenetics

Methylation balance
Methylase
Demethylase

Histone
H3 H4

Acetylation balance
HAT HDAC

William C. Aird Circ Res. 2007;100:158-173
Endothelial dysfunction

- Systemic pathological state of the endothelium
- **Imbalance** between vasodilating and vasoconstricting substances produced by the endothelium
- Shift of the balance in favour of vasoconstrictive, pro-inflammatory and pro-thrombotic effects
- Mainly due to reduced bioavailability and bioactivity of nitric oxide (NO)
Vasodilation

- Nitric oxide
- EDHF
- Prostacyclin
- Acetylcholine
- Bradykinin
Nitric oxide

• Most abundant free radical in the body
• Halflife of NO is affected by its chemical reaction and inactivation by superoxide anion

\[ \cdot O_2^- + \cdot NO \rightarrow ONOO^- \]
Shear stress

- A stress state where **the stress force is parallel** to the surface of the vessel (as opposed to normal stress, where the stress is vertical) – frictional force

- Force exerted on vessel wall / cross-sectional area

- NO is released after corrupted **shear stress** in the vessel – vasodilation

- NO mediated vasodilation restores shear stress

- If chronic – upregulation of inflammatory cytokines – endothelial dysfunction
Protective effects of NO

• Smooth muscle relaxation and vasodilation
• Lowering blood pressure
• Reducing proliferation of vascular smooth muscle
• Inhibition of platelet aggregation
• Inhibition of expression of VCAM and ICAM
Vasoconstriction

• Endothelin-1
• Prostaglandin H\textsubscript{2}
• Thromboxane A\textsubscript{2}
• ROS
• Endothelium-bound ACE – angiotensin II
Regulatory Functions of the Endothelium

**Normal**

- Vasodilation: NO, PGI2, EDHF, BK, C-NP
- Thrombolyis: tPA, Protein C, TF-I, vWF
- Platelet Disaggregation: NO, PGI2
- Antiproliferation: NO, PGI2, TGF-β, Hep
- Lipolysis: LPL

**Dysfunction**

- Vasoconstriction: ROS, ET-1, TxA2, A-II, PGH2
- Thrombosis: PAI-1, TF-α, TxA2
- Adhesion Molecules: CAMs, P,E Selectins
- Growth Factors: ET-1, A-II, PDGF, ILGF, ILs
- Inflammation: ROS, NF-κB
The endothelium maintains vascular health

Dilatation
Growth inhibition
Antithrombotic
Anti-inflammatory
Antioxidant

Constriction
Growth promotion
Prothrombotic
Proinflammatory
Pro-oxidant
What causes Endothelial Dysfunction?

Negatively Affect
- Smoking
- Diabetes
- High Blood Pressure
- High Cholesterol
- Weight Gain
- Mental Stress
- Excessive Inflammation

Positively Affect
- Exercise
- Weight Loss
- Stress Reduction
- Cholesterol-Lowering Drugs
Consequences of ED

• ED as progenitor of atherosclerosis (ED is present long before onset of symptoms)
• ED as predictor of future cardiovascular events

Fig. 1 From the causes to the consequences of endothelial dysfunction. CAD coronary artery disease, OSA obstructive sleep apnea, PAD peripheral artery disease
Oxidative stress

• **Imbalance** between production of **reactive oxygen species** and ability of the system to detoxify the reactive intermediates or to repair the damage

• Key mechanism of endothelial dysfunction

• OS + ED are major factors for atherosclerosis
Oxidative stress 

Endothelial dysfunction 
Reduced NO bioavailability 

Leukocyte adhesion & inflammation 
Lipid deposition 
Vascular smooth muscle cell proliferation 
Platelet aggregation & thrombosis 
Vasoconstriction 

Progression of atherosclerosis and cardiovascular disease
SOD = Superoxide Dismutase
CAT = Catalase
GPx = Glutathione Peroxidase
GR = Glutathione Reductase
L-Arg = L-Arginine
L-Cit = L-Citrulline
ONOO⁻ = Peroxynitrite
•ON = Nitric Oxide
O₂⁻ = Superoxide
H₂O₂ = Hydrogen Peroxide
H₂O = Water
GSH = Glutathione
GSSG = Glutathione Disulfide
ED in disease

- **Cardiovascular disease**
- Diabetes
- Transplant vasculopathy
- Autoimmune diseases
- Celiac disease and irritable bowel syndrome
- Hematologic disorders
- Neurocognitive disorders
- Cirrhosis
1. ED in diabetes

- T1DM, T2DM
- Pathogenesis unclear
- Multifactorial etiology of ED
- 1. Insulin resistance
- 2. Pro-inflammatory signalling
- 3. Oxidative stress
- 4. Protein kinase C
- 5. Hyperglycemia
Insulin resistance in ED

• Insulin activates vasoprotective pathways
  • PI3K/Akt – eNOS expression and activation

• In contrast, MAPK/ERK pathway promotes ET-1 and cellular proliferation

• In physiological conditions – PI3K predominates

• Insulin resistance – PI3K deficiency, MAPK predominates – proatherogenic signalling
Pro-inflammatory signalling in ED

- Adipose tissue produces inflammatory cytokines
- TNFalpha, free fatty acids, RAGE activate NFkB that further stimulates expression of inflammatory genes in endothelium
- Reduction of NO expression

Table 1. Inflammatory components of diabetes complications.

<table>
<thead>
<tr>
<th>Inflammatory cytokines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukins IL-1, IL-6, IL-18</td>
<td></td>
</tr>
<tr>
<td>Tumour necrosis factor-alpha (TNF-α)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adhesion molecules</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercellular adhesion molecule-1 (ICAM-1)</td>
<td></td>
</tr>
<tr>
<td>Vascular cell adhesion molecule-1 (VCAM1)</td>
<td></td>
</tr>
<tr>
<td>E-selectin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemokines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL-2 (MCP-1)</td>
<td></td>
</tr>
<tr>
<td>CX3CL1 (fractalkine)</td>
<td></td>
</tr>
<tr>
<td>CCL5 (RANTES)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transcription factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NFκB</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toll-like receptors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR2</td>
<td></td>
</tr>
<tr>
<td>TLR4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pro-fibrotic cytokines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transforming growth factor beta (TGF-β)</td>
<td></td>
</tr>
<tr>
<td>Connective tissue growth factor (CTGF)</td>
<td></td>
</tr>
</tbody>
</table>
Oxidative stress in ED

• OS as a unifying mechanism of endothelial injury
• OS leads to **diminished NO bioavailability**
  • Direct degradation of NO
  • Alterations in functional capacity of eNOS
2. ED in hypertension

- ED as an **early event** in pathophysiology of **essential hypertension** that contributes to subclinical target organ damage and progression of atherosclerosis
  - Defective endothelial L-arginine/NO pathway
  - Impaired responsiveness to exogenous NO
  - Reduced generation of platelet NO
  - In the presence of oxidative stress

- Pro-inflammatory, pro-atherosclerotic, pro-thrombotic phenotype
Mechanism of ED in hypertension

- Hypertension as **cause** rather than consequence of endothelial dysfunction
- Hypertension-induced oxidative stress
Measuring endothelial function

• 1950s – endothelium as a dynamic organ with diverse capabilities

• Invasive methods

• 1992 – Celermajer et al. proposed first non-invasive method for assessment of endothelial function - diameter of superficial femoral and brachial arteries
  • At rest
  • During reactive hyperemia (endothelium-dependent dilatation)
  • After sublingual nitroglycerin (endothelium-independent dilatation)
Vascular markers of ED

- Quantitative coronary angiography
- MRI
- PET
- Invasive measurement of forearm blood flow (FBF) by venous occlusion plethysmography
Vascular markers of ED

- Non-invasive measurement
  - **Flow-mediated dilation (FMD)** – macrovascular function
  - Peripheral arterial tonometry – microvascular function
  - Laser Doppler flowmetry
ED in periodontitis

The Treatment of Periodontitis and Endothelial Function

Table 1. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control-Treatment Group (N=59)</th>
<th>Intensive-Treatment Group (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>47.8±6.3</td>
<td>47.7±7.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>30 (51)</td>
<td>30 (49)</td>
</tr>
<tr>
<td>Smoking status — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>21 (36)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>18 (31)</td>
<td>19 (31)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20 (34)</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Family history of cardiovascular disease — no. (%)</td>
<td>40 (68)</td>
<td>38 (62)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>41 (69)</td>
<td>41 (68)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (10)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (17)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>27.3±5.4</td>
<td>27.2±5.0</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.5±17.4</td>
<td>125.6±15.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.2±11.1</td>
<td>80.5±11.4</td>
</tr>
<tr>
<td>Brachial-artery diameter — mm</td>
<td>3.6±0.6</td>
<td>3.7±0.8</td>
</tr>
<tr>
<td>Reactive hyperemia ratio§</td>
<td>8.9±4.1</td>
<td>8.8±4.2</td>
</tr>
<tr>
<td>Flow-mediated dilatation — %</td>
<td>6.5±2.6</td>
<td>7.1±4.2</td>
</tr>
<tr>
<td>Nitroglycerin-mediated dilatation — %¶</td>
<td>17.9±6.9</td>
<td>17.9±6.5</td>
</tr>
<tr>
<td>CRP — mg/liter</td>
<td>3.8±3.3</td>
<td>2.5±2.7</td>
</tr>
<tr>
<td>Interleukin-6 — pg/ml</td>
<td>2.1±3.9</td>
<td>2.4±5.4</td>
</tr>
<tr>
<td>Soluble E-selectin — ng/ml</td>
<td>20.3±13.6</td>
<td>19.6±14.0</td>
</tr>
<tr>
<td>t-PA — ng/ml</td>
<td>4.5±0.6</td>
<td>3.2±0.4</td>
</tr>
<tr>
<td>PAI-1 — ng/ml</td>
<td>21.39±1.8</td>
<td>21.5±1.5</td>
</tr>
<tr>
<td>Von Willebrand factor — IU/ml</td>
<td>0.87±0.16</td>
<td>0.90±0.19</td>
</tr>
<tr>
<td>Leukocyte count — x 10^3/liter</td>
<td>7.1±2.0</td>
<td>6.4±1.6</td>
</tr>
<tr>
<td>Cholesterol — mmol/liter</td>
<td>5.3±1.2</td>
<td>5.3±1.0</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>1.5±0.4</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>3.2±1.0</td>
<td>3.1±0.9</td>
</tr>
<tr>
<td>Glucose — mmol/liter</td>
<td>5.1±0.6</td>
<td>5.1±0.8</td>
</tr>
<tr>
<td>Triglycerides — mmol/liter</td>
<td>1.5±1.5</td>
<td>1.4±1.0</td>
</tr>
</tbody>
</table>
Figure 2. Flow-Mediated Dilatation and Nitroglycerin-Mediated Dilatation during the 6-Month Study Period.
CONCLUSIONS

Intensive periodontal treatment resulted in acute, short-term systemic inflammation and endothelial dysfunction. However, 6 months after therapy, the benefits in oral health were associated with improvement in endothelial function.
ED treatment

• Treatment should target the underlying comorbidity that lead to ED

• Life style modification – diet, exercise, smoking cessation, weight reduction

• NO pathways – L-arginine, PDE-I

• Receptor and enzyme pathways – beta blockers, ACE-I, angiotensin receptor blockers, statins, aspirin
Secondary endothelial therapy

- Preserve the function of the already injured endothelium to delay progression of cardiovascular disease

- Statins, ACE-I, beta blockers, endothelin antagonists
Control questions

• What are the 3 main vasodilators?
• Define shear stress
• How oxidative stress leads to ED?
• Which functions of endothelium are dysbalanced / predominate in ED?
• What is the standard method for measurement of endothelial dysfunction?
• Endothelial barrier dysfunction in septic shock
  https://www.youtube.com/watch?v=yl6R_3Jrs_s

• NO and vasodilation
  https://www.youtube.com/watch?v=echVKswxTqQ

• Vascular endothelium
  http://www.authorstream.com/Presentation/nitinpuram-1516566-vascular-endothelium/
A short break
Venous insufficiency
Varices
Venous system of lower limbs

- Superficial
- Perforator
- Deep
Chronic venous disease

• Condition in which the veins cannot pump enough blood back to the heart
• 20% of Western population

• Varicose veins
• Chronic venous insufficiency
Chronic venous disease

• Causes:
  • Deep vein thrombosis
  • Arteriovenous fistula
  • Phlebitis
  • Thrombophilia
  • Obesity
Varicose veins

• Dilated, often palpable, subcutaneous veins with reversed blood flow
• Mostly in legs
• 30% of population (18% men, 42% women)
• Risk factors: unknown, age, sex, pregnancy, obesity, family history
Pathogenesis

- Reflux
- Obstruction

- Varicose veins:
  - Increased amount of collagen
  - Decreased number of smooth muscle cells and elastin

- Disorganization of muscle components, disruption of elastin fibres and fibrosis

- Weakness of vein wall leads to dilatation and enlargement of the **valve ring** – the vein is unable to work properly - **reflux**
Pathogenesis

• **Descending** theory – the process starts proximally and expands distal

• **Ascending** theory – tributaries become dilated and incompetent and only thereafter the main trunks and junctions
Pathogenesis

• **Obstruction**

• **Acute** obstruction occurs in deep vein thrombosis
• **Chronic** obstruction caused by post-thrombotic changes – stenosis, occlusion, rigidity of vein wall

• Obstruction + reflux – in 55% of symptomatic patients
Figure 4. Contrasting Effects of Steady, Laminar Shear Stress (Panel A) and Turbulent or Reversing Shear Stress (Panel B) on Vessel Walls.
Evaluation

- **Clinical features**: swelling, stasis, skin changes, ulceration
- **Symptoms**: limb pain, itching, restless legs, nocturnal leg cramps, heaviness, discomfort
- Pain
Pain

- Assessed by **visual-analogue scale**, type and frequency of analgesic use
- Absent in 20% patients
- The only feature in 10% patients
- Is relieved by **leg elevation, support stockings, walking**
CEAP classification

- Clinical
- Etiologic
- Anatomical
- Pathophysiological

- CVI = C₃-C₆
Figure 1. Clinical Manifestations of Chronic Venous Disease.
Telangiectases (clinical, etiologic, anatomical, and pathophysiological [CEAP] class C₃) are shown in Panel A, varicose veins (CEAP class C₄) in Panel B, pigmentation (CEAP class C₅) in Panel C, and active ulceration (CEAP class C₆) in Panel D.
<table>
<thead>
<tr>
<th>Clinical class</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀</td>
<td>No venous disease</td>
</tr>
<tr>
<td>C₁</td>
<td>Spider Angioma</td>
</tr>
<tr>
<td>C₂</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>C₃</td>
<td>Edema of venous etiology</td>
</tr>
<tr>
<td>C₄</td>
<td>Hyperpigmentation, Dermatitis, Lipodermatosclerosis.</td>
</tr>
<tr>
<td>C₅</td>
<td>Healed ulceration</td>
</tr>
<tr>
<td>C₆</td>
<td>Active ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aₛ</td>
<td>Superficial Veins</td>
</tr>
<tr>
<td>Aₒ</td>
<td>Deep Veins</td>
</tr>
<tr>
<td>Aₚ</td>
<td>Perforating Veins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pᵣ</td>
<td>Reflux</td>
</tr>
<tr>
<td>Pₒ</td>
<td>Obstruction</td>
</tr>
<tr>
<td>Pᵣₒ</td>
<td>Reflux &amp; obstruction</td>
</tr>
</tbody>
</table>
### Table 2. Venous Clinical Severity Score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1 (mild)</th>
<th>2 (moderate)</th>
<th>3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional; no use of analgesics</td>
<td>Daily; occasional use of non-narcotic analgesics</td>
<td>Constant use of narcotic analgesics</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>None</td>
<td>Few, scattered</td>
<td>Multiple</td>
<td>Extensive</td>
</tr>
<tr>
<td>Edema</td>
<td>None</td>
<td>Evening, ankle only</td>
<td>Afternoon, above ankle</td>
<td>Morning above ankle</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>None</td>
<td>Limited</td>
<td>Diffuse over lower third of leg</td>
<td>Wide distribution</td>
</tr>
<tr>
<td>Inflammation and cellulitis</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Focal</td>
<td>Less than lower third of leg</td>
<td>Entire lower third of leg or more</td>
</tr>
<tr>
<td>Active ulcers — no.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Duration of active ulceration — mo</td>
<td>None</td>
<td>&lt;3</td>
<td>3–12</td>
<td>Not healed at &gt;12</td>
</tr>
<tr>
<td>Diameter of active ulcer — cm</td>
<td>None</td>
<td>&lt;2</td>
<td>2–6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Use of stockings</td>
<td>None</td>
<td>Occasional</td>
<td>Most days</td>
<td>Constant</td>
</tr>
</tbody>
</table>

* An aggregate score for the limb is calculated by adding the individual component scores. The range of the total score is 0 to 30.
Imaging

- Duplex ultrasound scan
Complications

- Deep vein thrombosis
- Skin changes
- Thrombophlebitis – thrombus in superficial vein
- Leg ulcers (3% patients)
- Bleeding
Treatment

Varicose veins: diagnosis and management

Clinical guideline
Published: 24 July 2013
nice.org.uk/guidance/cg168

Editor’s Choice — Management of Chronic Venous Disease

Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

Writing Committee

ESVS Guidelines Committee
P. Kolh, G.J. de Borst, N. Chakfé, S. Debus, R. Hinchliffe, I. Koncar, J. Lindholt, M.V. de Ceniga, F. Vermassen, F. Verzini,

Document Reviewers
M.G. De Maeseneer, L. Blomgren, O. Hartung, E. Kalodiki, E. Korten, M. Lugli, R. Naylor, P. Nicolini, A. Rosales
Treatment

• Goals:
  • Alleviate symptoms
  • Prevent severe complications (ulcers)

• 1. Endothermal ablation of the saphenous vein – burn the vein from inside (radiofrequency or laser)
• 2. Foam sclerotherapy
• 3. Surgery
• 4. Compression hosiery (only if no other intervention is suitable)
Advice

• Weight loss
• Light to moderate physical activity
• Avoid factors that make symptoms worse
• When and where to seek further medical help
Treatment in pregnancy

• Pregnancy can exacerbate symptoms of varicose veins and cause new ones

• **No intervention** in pregnancy (increases risk of thrombosis)

• Compression hosiery should be used
Flowchart 'Management of chronic venous disease'

1. Patient
2. History (QoL)
3. Clinical exam (VCSS, CEAP) + DUPLEX of the superficial and deep venous system
   - C0-C6: Superficial vein pathology
     - Saphenous incompetence
       - Thermal ablation
       - Non-thermal ablation
       - Conservative
     - Tributary incompetence
       - Sclerotherapy
       - Foam sclerotherapy
       - Phlebectomy
       - Conservative
   - C0-C6: Deep vein pathology
   - Vascular malformations
   - Consider Rx of superficial pathology first if also present
   - Multidisciplinary approach
   - Deep Venous Obstruction
   - Deep Venous Incompetence
     - Conservative
     - Stenting
     - Endophlebectomy
     - AV fistula
     - Conservative
     - Valvuloplasty
     - Valve/VEin transposition
     - Neovalve
Control questions

- Two mechanisms of CVI
- What does CEAP mean?
- What is the link between CVI and ED?
- Diagnostic methods
- How to know the most up-to-date methods of therapy?