Beside the large vessels – microvascular disorders in critical limb ischaemia

Katja S. Mühlberg
University of Leipzig
Department of Neurology, Internal Medicine and Dermatology
Disclosure

Speaker name:
Katja S. Mühlberg

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

I do not have any potential conflict of interest
Beside the large vessels...

- MEDIUM SIZED ARTERIES
  Mediasclerosis

- SMALL ARTERIES
  major site of autonomic regulation of blood flow

- including ARTERIOLES
  hyaline arteriolar sclerosis with age, diabetes and hypertension

- CAPILLARIES
  nutritional function, AV-shunts
Beside the large vessels...

→ medium sized and small vessels

**Atherosclerosis**

J. G. Mönckeberg: *Über die reine Mediaverkalkung der Extremitätarterien und ihr Verhalten zur Arteriosklerose.*
In: *Virchows Archiv.* Jg. 1903, S. 141–167

**Mönckeberg’s Mediasclerosis**

**Intima**

**Media**

**Consequences**

Occlusion of artery
Vascular stiffness (non-occlusive?)

*does not obstruct arterial flow because intima is not involved*


*Proudfoot D. Herz. 2001;26:245-251*
Beside the large vessels...

- loss of elasticity of arterial wall
  - (falsely) high ankle blood pressure
  - decreasing propulsion of the antegrade flow
  - ultimate stasis
  - thrombus formation in small vessels

Despite of large vessel revascularisation:
- critical reduction of tissue perfusion pressure and nutritive blood supply
Beside the large vessels...

- loss of elasticity of arterial wall
  - (falsely) high ankle blood pressure
  - decreasing propulsion of the antegrade flow
  - ultimate stasis
  - thrombus formation in small vessels

- disturbed autoregulation/neuropathy

Σ impaired arterial remodelling

adapted from Netter

Beside the large vessels...  → small vessels, arterioles

Hyaline & hyperplastic arteriolosclerosis

- less than 4 layers of smooth muscle cells, total diameter 100 microns or less
- the layers become progressively less distinct as the arteries get smaller
- are the major site of autonomic regulation of blood flow

<table>
<thead>
<tr>
<th>Normal</th>
<th>Hyaline arteriolosclerosis</th>
<th>Hyperplastic arteriolosclerosis</th>
</tr>
</thead>
</table>

hyaline deposition in the intima and media with luminal narrowing
concentric proliferation of smooth muscle cells with luminal narrowing („onion-skin“)
Beside the large vessels...

**Hemorheology**

DEFORMABILITY of RBC: erythrocytes must change their shape extensively while passing through microcirculation. In diabetics this is restricted by:
- glycosylated cytoskeletal proteins of RBCs
- elevated serum ferritin levels
- oxidative stress caused by increased iron leading to eryptosis (suicidal cell death)

RBC of a healthy individual within a normal fibrin network

RBC of a diabetic patient where the RBC is entrapped in atypical fibrin fibers (fibrin clots abnormally)

*Pretorius E et al. Integr. Biol., 2014, 6, 486*
各种机制促进纤维蛋白原的促进动脉粥样硬化和血栓形成：
(a) 增加血液粘度
(b) 可恢复RBC聚集
(c) 血小板聚集
(d) 纤维蛋白原降解产物（FDPs）与LDL结合并捕获更多纤维蛋白原
(e) FDP刺激平滑细胞增殖和迁移

Hemorheology

Hypercoagulability
- elevated levels of plasma fibrinogen

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.4</td>
<td>56.4</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>324 ± 139</td>
<td>656 ± 130</td>
</tr>
<tr>
<td>HbAlc (%)</td>
<td>4 ± 1.6</td>
<td>8.5 ± 1.69</td>
</tr>
</tbody>
</table>
Beside the large vessels...

Hemorheology

Hypercoagulability

- dysbalance between PGI$_2$ and TXA$_2$

Healthy

DM II
Increased serum ferritin and other iron parameters

- Fe$^{3+}$ chelating agents
- Free radical scavengers

Prothrombin → Thrombin → FIBRINOGEN

- Soluble fibrin monomers
- Soluble ‘parafibrin’

Linear polymerization forming fibrin nets around RBCs

Lateral aggregation forming fibrin mats trapping RBCs
Beside the large vessels... ➔ capillaries

The role of pericytes

- contractile cells with a “spider-like” shape found on the outside of the small vessels
- they accompany and support microvasculature
• diabetes alters the cross-talk between pericytes and endothelial cells.
• pericyte loss contributes to abnormal endothelial function
Beside the large vessels...

endoneurinal microvessels of diabetics:
• decrease in pericyte coverage
• basement membrane thickening and reduplication
  → degenerativ changes in microvasculature
  → disruption of blood-nerve-barrier
  → further loss of pericytes
  → impaired nerve blood flow and hypoxia

Beside the large vessels...

Hyperglycaemia and hyperinsulinaemia induced changes in pericyte biology. Hyperglycaemia alters pericyte function and phenotype, induces pericyte apoptosis leading to pericyte loss and impaired neovascularisation, moreover hyperglycaemia contributes to endothelial dysfunction, which further adds to pericyte loss and impaired neovascularisation. However, pericytes themselves play an active role in this pathogenesis (red), by secretion of pro-angiogenic factors, fibronectin, and collagen IV, thereby contributing to basement membrane thickening, neovascularisation and pericyte apoptosis. To which extent hyperinsulinaemia is conducive to pericyte loss remains elusive (Another contributing factor are elevated levels of plasma fibrinogen.)
Beside the large vessels...

- pericytes
Beside the large vessels...

- skin microvascular dysfunction is regulated by
  - endothelial factors: NO, prostanoids,...
  - non-endothelial factors: smooth muscle cells, pericytes,...

Thermo-regulating arterio-venous shunt vessels are innervated by sympathetic nerves. In diabetics disturbances are found despite a normal or even increased total blood supply.
Beside the large vessels...

- skin microvascular dysfunction

The total skin microcirculation is normal (or even overperfused), while the capillary circulation is markedly reduced.

( the warm and red feet of peripheral neuropathy!!)

**tissue viability in CLI?**

- in autonomic neuropathy AV-shunts stay open
- reduced capillary blood flow is due to the arterio-venous shunting, bypassing the nutritional skin capillaries
Beside the large vessels...

- despite of well perfused large vessels
- despite of warm and red feet
- despite of normal or elevated ABI/toe pressure

→ there is a need in estimating local tissue viability in diabetic patients with CLI, e.g. by tcPO₂-measurement laser doppler fluxmetrie
Beside the large vessels...

• despite of well perfused large vessels
• despite of warm and red feet
• despite of normal or elevated ABI/toe pressure

→ there should be a lower threshold for revascularization in diabetic patients with CLI, including the spectrum of:
  • endovascular/interventional procedures
  • surgical procedures

• therapeutic strategies in CLI without options for revascularisation:
  prostaglandins
  low-dose urokinase
  intermittent pneumatic compression

Weck M. Ther Adv Endocrinol Metab (2011) 2(6) 247-555
Beside the large vessels...

• despite of well perfused large vessels  
• despite of warm and red feet  
• despite of normal or elevated ABI/toe pressure

• always conservative procedures

• offloading techniques  
• outpatient wound care  
• patient education  
• postinterventional reviews and  
• follow-ups

The diabetic foot patient will be your patient not only for the time of ulcer healing or CLI. He belongs to you for the rest of his life.
… by the way…

Johann Georg Mönckeberg (1877-1925)
German pathologist

„My Life was happy from the beginning to the end“
Thank you for your attention & have a nice time in Leipzig

“You’re right! Leipzig’s the place for me! ’Tis quite a little Paris; people there Acquire a certain easy finish’d air.”

J. W. v. Goethe
Faust I
Beside the large vessels – microvascular disorders in critical limb ischaemia

Katja S. Mühlberg
University of Leipzig
Department of Neurology, Internal Medicine and Dermatology