Getting small blood cells through small gaps; what could go wrong?

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The pumbing (dual circuit)
Blood - the ‘liquid’

Getting the blood around the circulation: different properties affect flow in different vessels

Small artery (~mm)

Arteriole (~100μm)

Capillary (<10μm)
........... getting small cells through small gaps

**Lung**
- alveolar wall
- alveolus
- alveolus (air space)
- endothelial cell nucleus
- capillary

**Spleen**

**Muscle**
It's not just red blood cells

Ulf Bagge, PhD Thesis, Goteborg 1975
It's not just squeezing through vessels ..........

.......... it's sticking and crawling out
Circulation of neutrophils

**Arteriole**
- Capillary
- **Venule**

Phagocytosis
- Killing
- Remodelling
- Apoptosis

Endothelial lining

White blood cell recruitment across the vessel wall

- Leukocyte
- Capture/Rolling
- Stabilisation
- Spreading
- Migration

Stimulatory signal
- (infection, trauma ....)

Flow
Neutrophils rolling or migrating on ‘inflamed’ endothelium

Low dose

High dose

Tumour necrosis factor
Getting small blood cells through small gaps; what could go wrong?

‘Clinical blood cell rheology’

Red blood cells: mechanics

Cellular mechanical factors affecting deformation

CELL GEOMETRY  

Surface area:volume ratio → ability to adapt shape

MEMBRANE (rigidity)

CYTOPLASM (concentrated haemoglobin solution)
Irreversibly Sickled Cells:
Surface area/volume  ↑ x1.25 (Shrunken)
Membrane rigidity  ↑ x2
Membrane viscosity ↑ x2.5

Endogenous
Induced by cyclical deoxygenation

Ca**-dependent K+ efflux (Gardos effect)
Protection by Ca++-channel blocker Nitrendipine

A. Relative Flow Resistance

B. Pore Clogging Particles

<table>
<thead>
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<th>Nitrendipine (M)</th>
<th>0</th>
<th>10^{-5}</th>
<th>10^{-4}</th>
<th>10^{-3}</th>
<th>10^{-2}</th>
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<tbody>
<tr>
<td></td>
<td>125</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>0</td>
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** Significant difference

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21/03/2014
Decreasing oxygen tension (HbS polymerisation/sickling)

Rigidity $\uparrow \times 5-100$

Deformation rate $\downarrow \times 50-200$
Plasmodium falciparum malaria

Sequestered in microcirculation
Adhered to endothelium?
Lodged in capillaries?
Adhesive receptors?
Effect of proteins inserted into the red cell membrane revealed by genetic manipulation of the parasite

Getting small blood cells through small gaps; what could go wrong?

Red blood cells: adhesion
Parasitised red cells can mimic ability of white cells to roll and stop on endothelium

Sequestration in blood capillaries key to pathogenesis?

Platelets

Endothelial cells

Sickle cells can also adhere to endothelium from flow

Adhesion may delay sickle cells in microvessels
Along with dehydration this allows sickling
Outcome – log-jam of rigid cells causing occlusion
Getting small blood cells through small gaps; what could go wrong?

White blood cells: mechanics

'S Activated' neutrophils
Effect of exposure to cigarette smoke

Small vessel inflammation (vasculitis) associated with anti-neutrophil cytoplasm antibodies (ANCA)

**Cytoplasmic (c-) ANCA:**
- Coarse granular staining
- Specificity for proteinase 3 (PR3)
- Most commonly associated with Wegener’s granulomatosis

**Perinuclear (p-) ANCA:**
- Staining restricted to sites around the nucleus
- Specificity for myeloperoxidase (MPO)
- Most commonly associated with microscopic polyarteritis
ANCA derived from plasma of patients with vasculitis causes rigidification of neutrophils

Effect of surgical interruption of blood flow (ischaemia and reperfusion)

Healthy control After repair of aortic aneurysm
Flow resistance of neutrophils after acute myocardial infarction

Peripheral vascular disease - chronic ischaemia of the leg

X-ray - Angiograms
Relative filtration rate

Filtration rate of neutrophils: isolated before and after amputation

Activation of neutrophils may cause problems **systemically** as well as in affected ischaemic tissue

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**White blood cells: adhesion and migration**
(at the wrong time/wrong place)
ANCA causes rolling neutrophils to become stationary adherent

ANCA also promotes migration across endothelium

ANCA contribution to pathology of vasculitis?
Combined with ............. ?
Exposure of endothelial cells to hypoxia and re-oxygenation

→ adhesion of flowing neutrophils on return of oxygen

<table>
<thead>
<tr>
<th>Conditioning pO$_2$ (60min)</th>
<th>150 (air)</th>
<th>25 (mild)</th>
<th>13 mmHg (severe hypoxia)</th>
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</thead>
<tbody>
<tr>
<td>Adherent neutrophils (/mm$^2$)</td>
<td>0</td>
<td>100</td>
<td>300</td>
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</table>

Hypoxia/reoxygenation one driver of neutrophil infiltration

Atherosclerosis - vicious cycle of leukocyte activation?
Clinical blood cell rheology – therapeutic lessons?

Sickle cell disease
Shrinking as a key factor in flow impairment
(deformability, polymerisation, adhesion)

Malaria
Inhibit sequestration to attack the parasite life-cycle

Leukocytes and vascular disease:
Don’t let them get too excited
Quieten them down
Stop them sticking

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