

Physiopathologie de la drépanocytose : quoi de neuf ?

... globules rouges drépanocytaires, endothélium
et hyperhémolyse

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Réseau des hémoglobinopathies



Bruxelles 15 Février 2008

The vascular endothelium

Barrier between blood and the subendothelial structures

Crucial role in controlling

- vascular tone
- thrombogenesis
- vascular remodeling

Numerous secretory properties

- anti- / pro-coagulant proteins
- vasodilators (NO) / vasoconstrictors (Et-1)
- growth factors

Expressing membrane receptors

- cell adhesion

Activated by various stimuli

- hypoxia
- inflammatory cytokines

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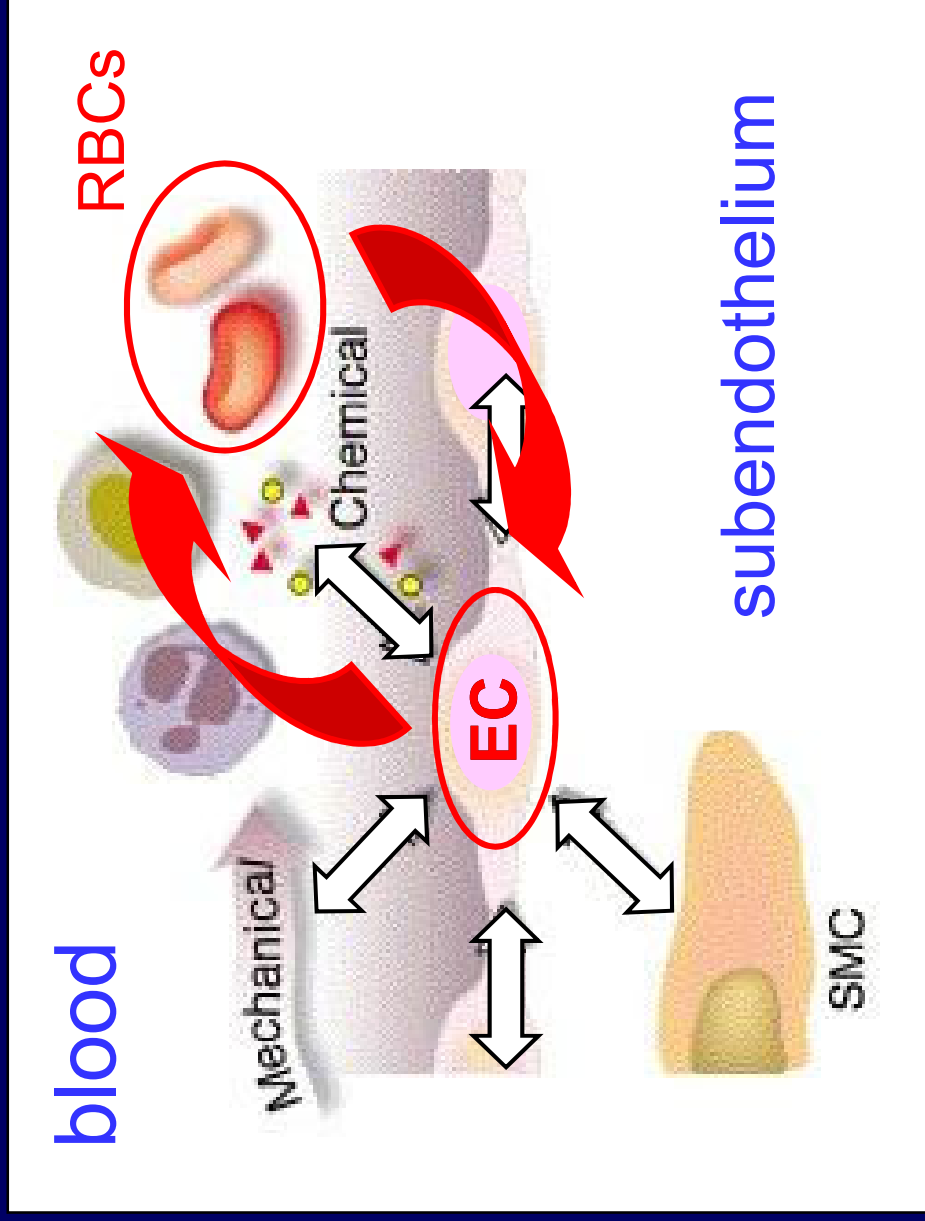
→ cell adhesion

Activated by various stimuli

hypoxia

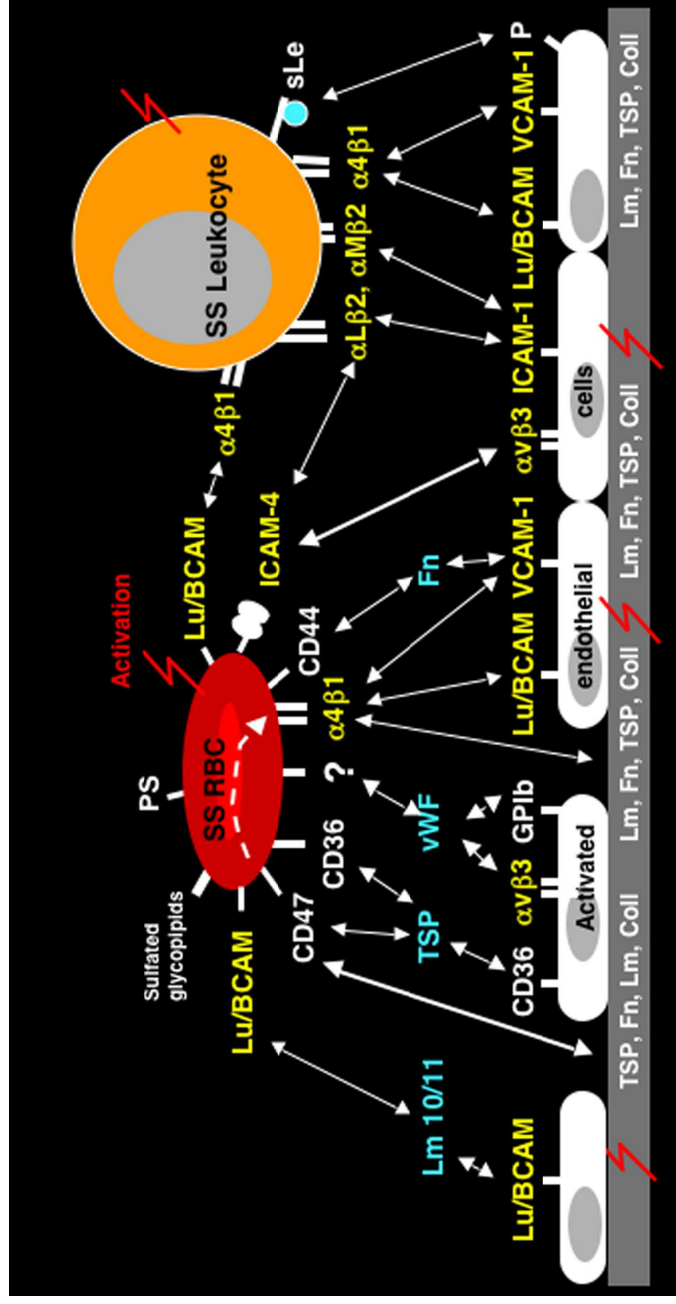
inflammatory cytokines

Interactions between the endothelium and circulating blood cells play a central role in vascular biology



In Sickle Cell Disease

abnormal cell adhesion to the endothelium plays a major in targetting vaso-occlusion



from JP Cartron

SCADHESION project C Le Van Kim, PL Tharaux, J Elion

....but so does the vascular tone

Endothelium-derived nitric oxide (NO) is a major actor of vascular biology

- vasodilation
- inhibition of platelet activation
- endothelial expression of adhesion molecules

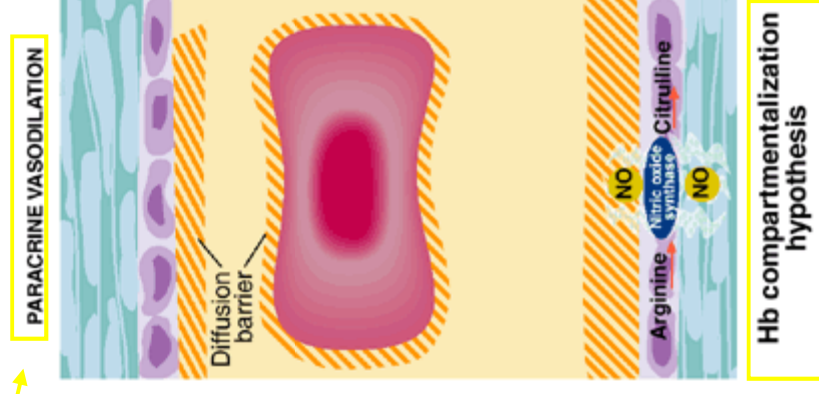


NO activates the soluble guanylate cyclase (sGC) in smooth muscle cells → vasodilation

Haemoglobin is the most potent NO scavenger

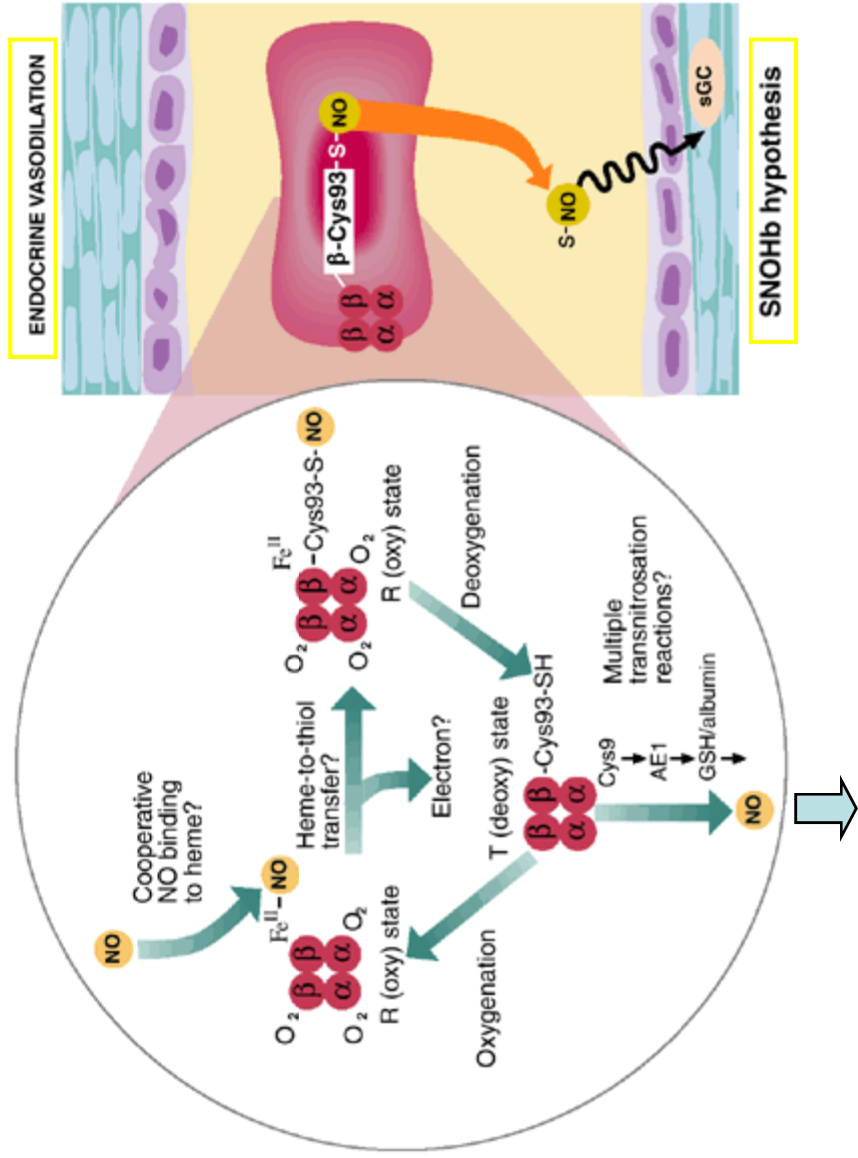
→ paradox at NO working as a diffusible effector and its proximity to large amounts of Hb in the RBC

but physiologically, physical and dynamical barriers prevent NO destruction by Hb

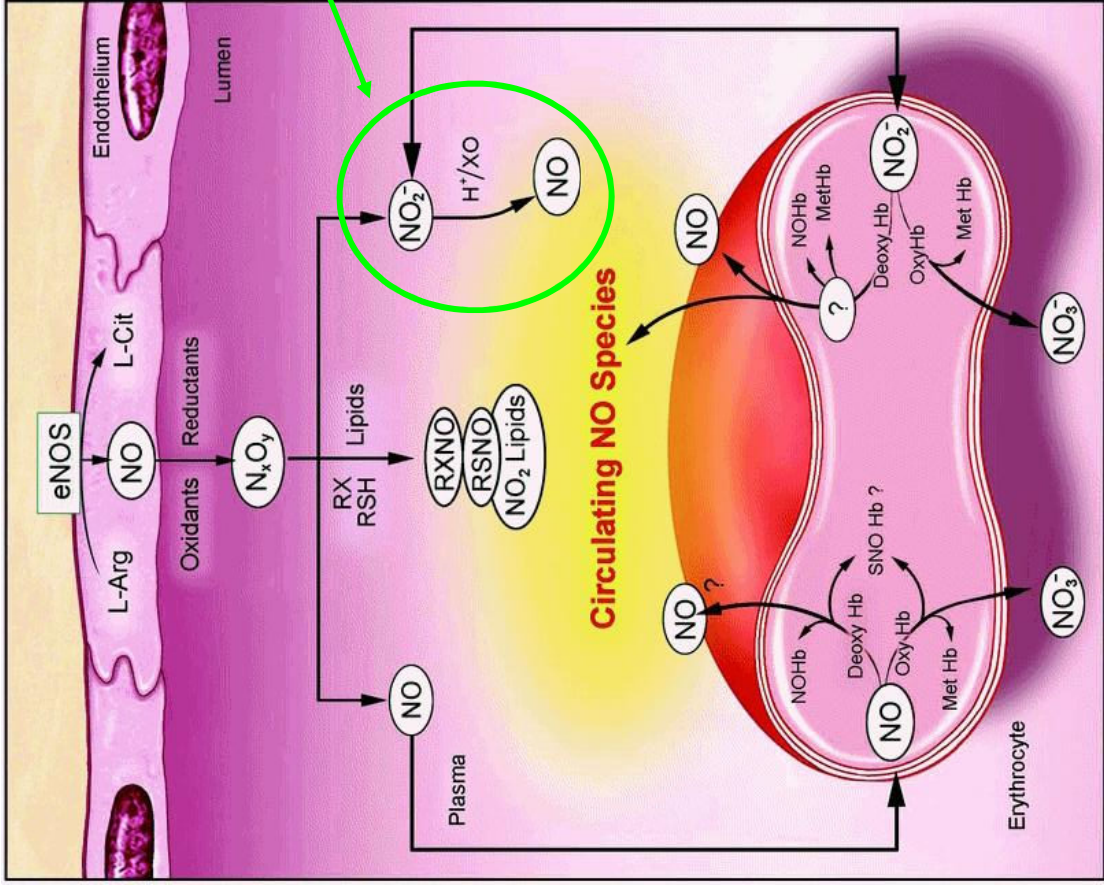


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and rather Hb in the RBC acts as a NO transporter



NO release in hypoxic tissues



Nitrites may act as a second important NO transporter



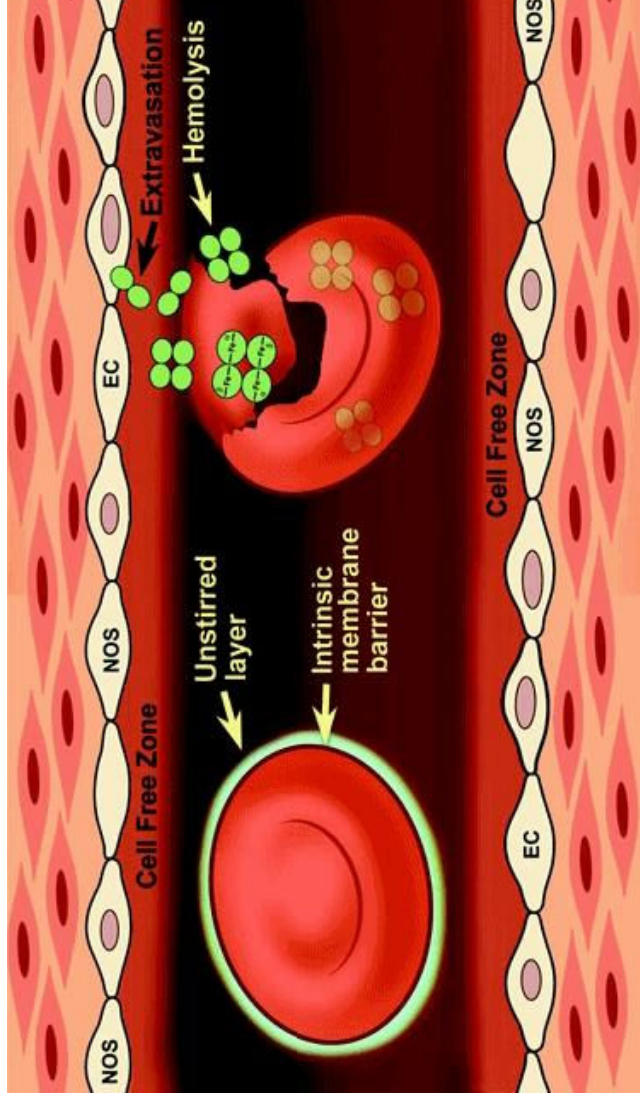
Paracrine vasodilation

Gladwin et al. Nature Medicine, 2003

Haemolysis

NO reacts 1,000 times more rapidly with free Hb than with RBCs

→ NO scavenging is complete



The normal balance of vasoconstriction/vasodilation is skewed toward vasoconstriction

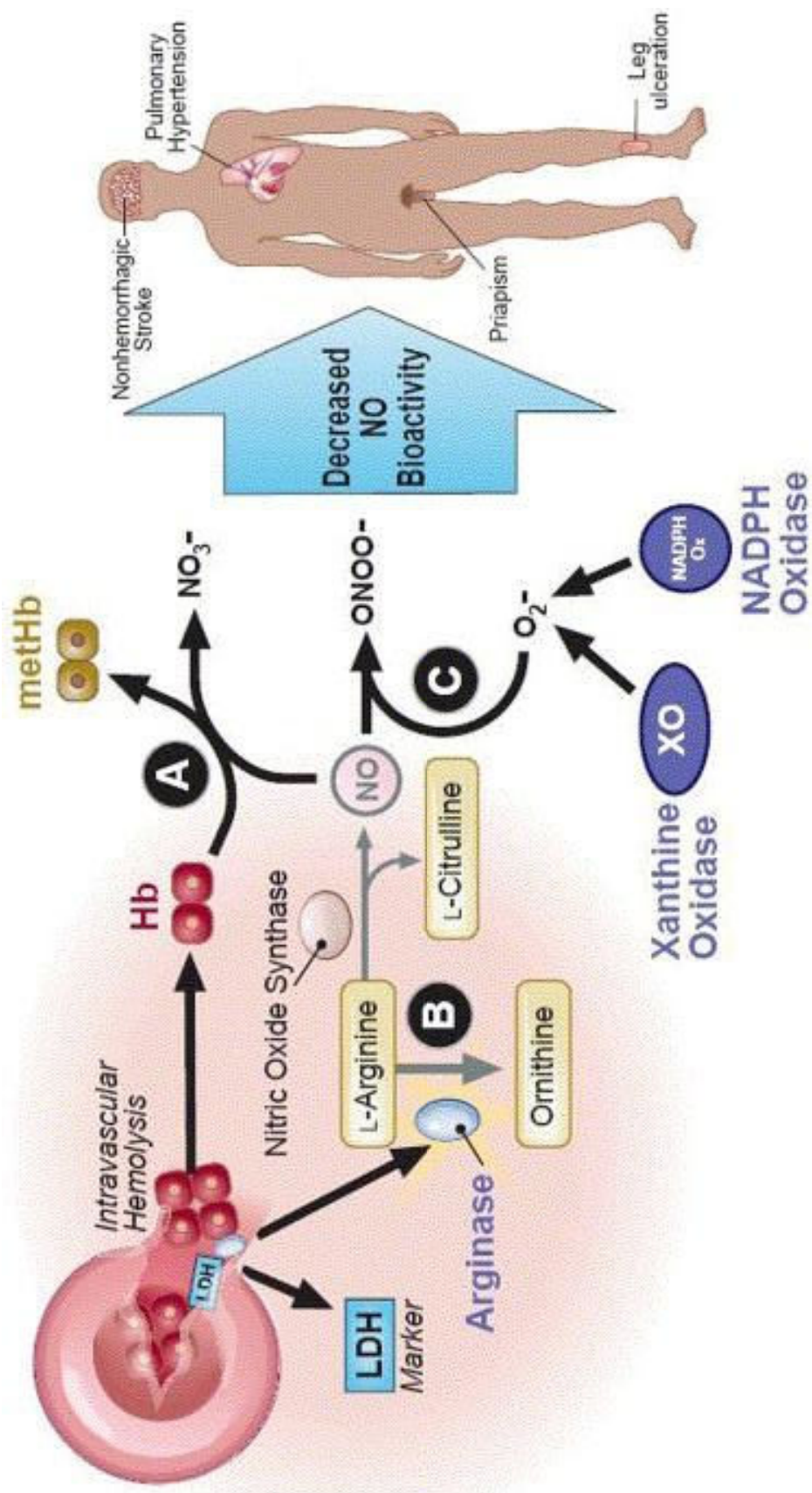
Thus in Sickle Cell disease:

haemolysis which has long been discounted when compared to
vaso-occlusion

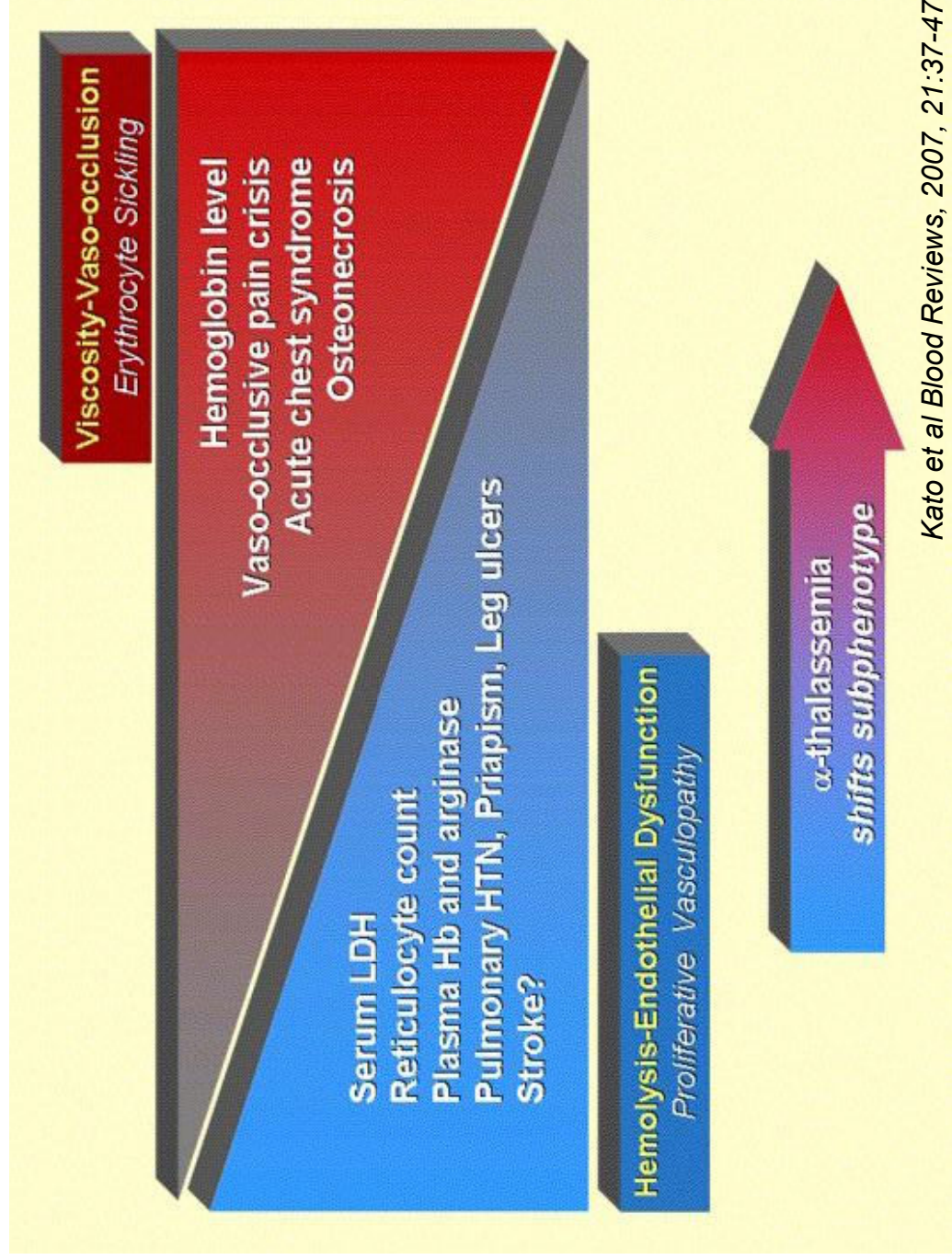
may actually be the proximate cause

of common vascular complications:

Pulmonary hypertension, cutaneous ulceration, acute and chronic
renal failure, priapism, stroke?

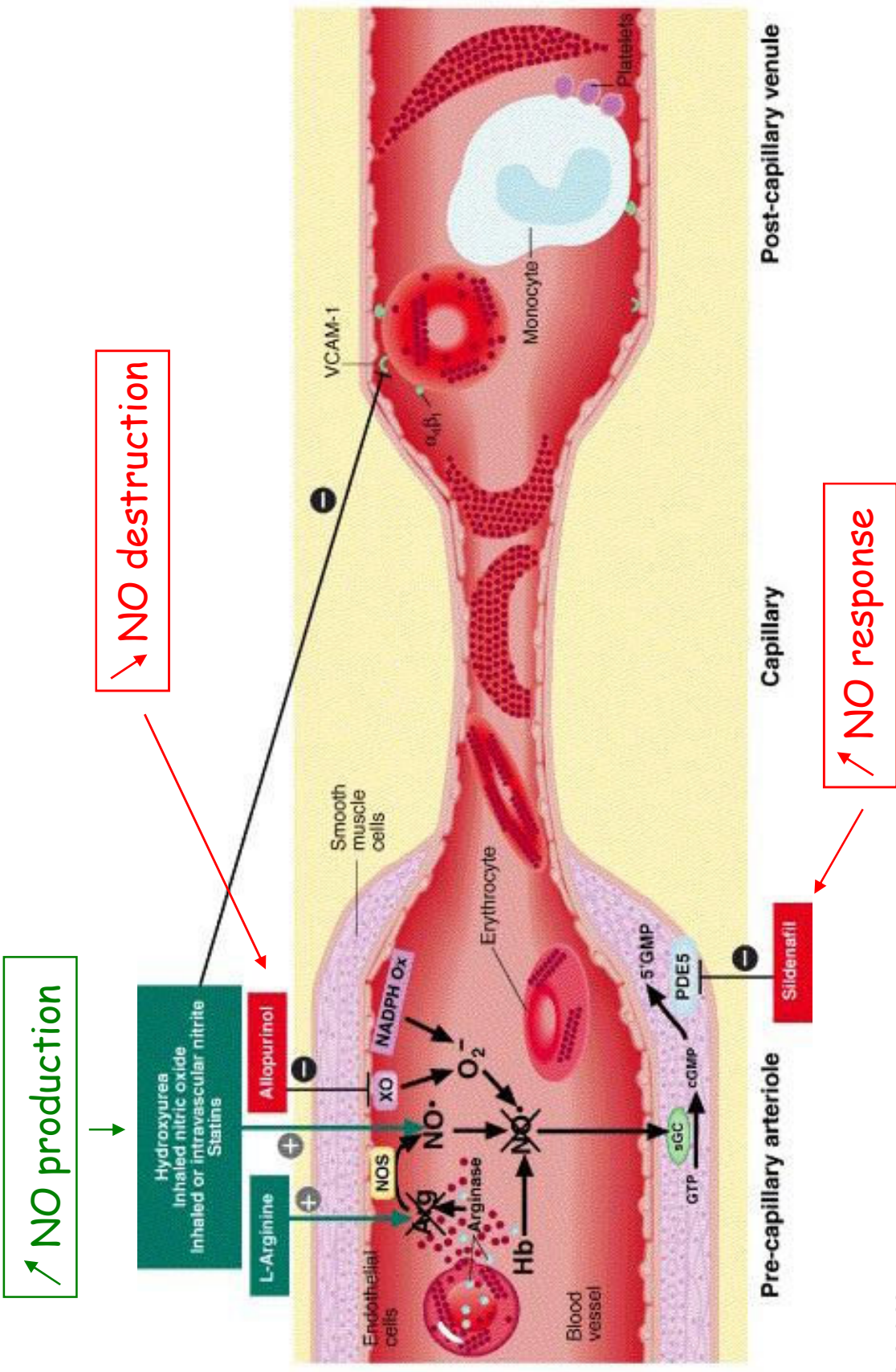


Two overlapping sub-phenotypes in SCD?



Kato et al Blood Reviews, 2007, 21:37-47

Therapeutic implications



Conclusions

Practice Points

Clinicians should be alert to a syndrome of haemolysis-endothelial dysfunction, including high serum LDH, pulmonary hypertension, leg ulcers and priapism

Research Prospects

Role of oxidant stress in reducing NO bioactivity in SCD

Efficacy of endothelin receptor antagonist bosentan or PDE-5 inhibitors in haemolysis-associated pulmonary hypertension

Efficacy of novel NO donors in acute and chronic SCD ischemic tissue injury