Regulation of red blood cell deformability is independent of red blood cell-nitric oxide synthase under hypoxia

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Abstract: The aim was to study impacts of mild to severe hypoxia on human red blood cell (RBC)-nitric oxide synthase (NOS)-dependent NO production, protein S-nitrosylation and deformability. Ambient air oxygen concentration of 12 healthy subjects was step-wisely reduced from 20.95% to 16.21%, 12.35%, 10% and back to 20.95%. Additional in vitro experiments involved purging of blood ($\pm$ sodium nitrite) with gas mixtures corresponding to in vivo intervention. Vital and hypoxia-associated parameters showed physiological adaptation to changing demands. Activation of RBC-NOS decreased with increasing hypoxia. RBC deformability, which is influenced by RBC-NOS activation, decreased under mild hypoxia, but surprisingly increased at severe hypoxia in vivo and in vitro. This was causatively induced by nitrite reduction to NO which increased S-nitrosylation of RBC α - and β -spectrins –a critical step to improve RBC deformability. The addition of sodium nitrite prevented decreases of RBC deformability under hypoxia by sustaining S-nitrosylation of spectrins suggesting compensatory mechanisms of non-RBC-NOS-produced NO. The results first time indicate a direct link between maintenance of RBC deformability under severe hypoxia by non-enzymatic NO production because RBC-NOS activation is reduced. These data improve our understanding of physiological mechanisms supporting adequate blood and, thus, oxygen supply to different tissues under severe hypoxia.

Keywords: Humans, nitric oxide, normobaric hypoxia, red blood cells, red blood cell deformability, red blood cell-nitric oxide synthase

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