Aged vs. fresh blood for the treatment of hemorrhagic shock; differential effect on liver outcome and possible mechanism

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Background & Aims Concerns have recently been raised about the safety and efficacy of transfusing stored red blood cells. Increased risk of post-transfusion complications has been reported with increasing "age"' of blood[1]. The liver is a target for injury in low flow states associated with trauma and hemorrhage[2]. The aim of the present study was to evaluate the effect of the age of transfused blood on liver injury and to explore possible mechanisms in a rat model.

Methods Anesthetized rats were randomized to either control group (CG; sham), hemorrhagic shock group (HSG) [controlled bleeding to a mean arterial pressure (MAP) of 25 mmHg] or resuscitation groups (10 min following controlled hemorrhage as in HSG, resuscitation with fresh blood (BRG-d0) or blood stored for 4 days or 7 days (7 ml, 1 ml/min). Liver injury was evaluated using fMRI combined with hypercapnia and hyperoxia for perfusion analysis (ΔS maps) as described[2,3], liver enzymes, apoptosis and liver histology. To explore possible mechanisms linking adverse liver outcome with increased duration of blood storage, we evaluated 2,3 DPG, reactive oxygen species, IL-1β, and TNFα levels in the transfused blood, as well as red blood cell deformability, aggregation and adhesion to the endothelium.

Results *Liver outcome following blood transfusion:* Resuscitation with fresh blood significantly attenuated liver injury induced by hemorrhagic shock as reflected by the significantly lower liver enzymes levels in serum, reduced liver injury on histology examination and significant reduction in apoptosis. Both fMRI and liver enzymes showed significant differences between resuscitation with fresh blood (BRG-d0) vs. blood stored for both 4 and 7 days (BRG-d4 and BRG-d7). However, significant aggravation of liver injury on histological examination and increased apoptosis were only observed following transfusion of blood stored for 7 days.

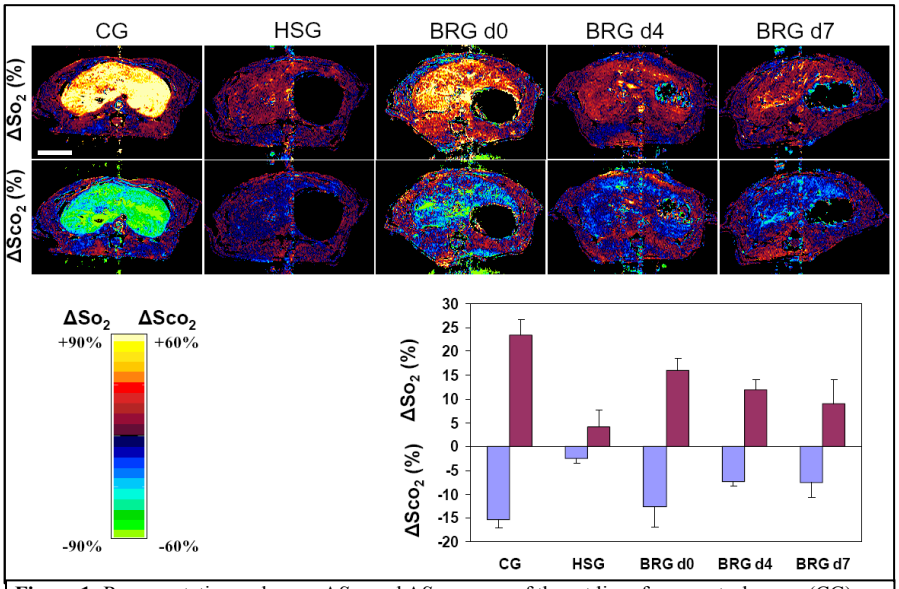

Figure 1: Representative and mean ΔSo_2 and ΔSco_2 maps of the rat liver from control group (CG), animals that underwent acute bleeding (HSG) and from animals resuscitated with fresh blood (BRG-d0), or blood stored for 4 or 7 days (BRG-d4/7).

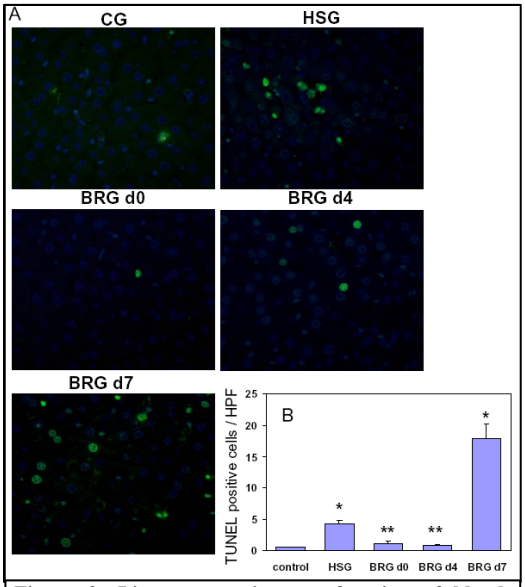

Figure 2: Liver apoptosis as a function of blood-storage duration. A. representative images of apoptotic cells in each group (green x400). **B**. Number of TUNEL-positive cells per high power field (N=6 rats/group).

Analysis of parameters of the stored blood: Analysis of blood samples stored for 0, 1, 4, 7, 11 and 14 days showed that 2,3-DPG levels were significantly reduced already at 4 days of blood storage, in good agreement with fMRI results. Blood levels of TNFα and reactive oxygen species did not change with time of storage, while IL-1β levels were significantly elevated already after 1 day of storage. Red blood cell deformability was considerably reduced only at 7 days into the storage period inducing a 5-fold increase in the number of rigid, undeformable cells, whereas RBC/endothelial cells adherence was not significantly affected by the increased storage time up to 7 days.

Conclusions In rats with acute bleeding, transfusion of blood stored longer than 4 days increased liver injury. This was associated with significant changes in the viscoelastic characteristics of the stored erythrocytes and probably unrelated the TNFα, IL-1β, reactive oxygen species, 2,3-DPG levels in the stored blood or the RBC/endothelial cells adherence properties. As transfusion of fresh stored blood is not an available option owing to blood shortages and current blood banking practices, our findings suggest a potential treatment target to reduce transfusion-related injury.

References: [1]Weinberg JA, J Trauma. 65(2):279, 2008; [2]Matot I, et al. Shock, 29(1):16, 2008; [3]Barash H, Radiology 243(3):727, 2007.