ERYTHROCYTE STORAGE INCREASES RATES OF NO AND NITRITE SCAVENGING: IMPLICATIONS FOR TRANSFUSION-RELATED TOXICITY

Ryan Stapley, Benjamin Y Owusu, Angela Brandon, Marianne Cusick, Cilina Rodriguez, Marisa B Marques, Jeffrey D Kerby, Scott R Barnum, Jordan A Weinberg, Jack R Lancaster, et al.[1]

Abstract

Storage of erythrocytes in blood banks is associated with biochemical and morphological changes to RBCs (red blood cells). It has been suggested that these changes have potential negative clinical effects characterized by inflammation and microcirculatory dysfunction which add to other transfusion-related toxicities. However, the mechanisms linking RBC storage and toxicity remain unclear. In the present study we tested the hypothesis that storage of leucodepleted RBCs results in cells that inhibit NO (nitric oxide) signalling more so than younger cells. Using competition kinetic analyses and protocols that minimized contributions from haemolysis or microparticles, our data indicate that the consumption rates of NO increased ~40-fold and NO-dependent vasodilation was inhibited 2-4-fold comparing 42-day-old with 0-day-old RBCs. These results are probably due to the formation of smaller RBCs with increased surface area: volume as a consequence of membrane loss during storage. The potential for older RBCs to affect NO formation via deoxygenated RBC-mediated nitrite reduction was also tested. RBC storage did not affect deoxygenated RBC-dependent stimulation of nitrite-induced vasodilation. However, stored RBCs did increase the rates of nitrite oxidation to nitrate in vitro. Significant loss of whole-blood nitrite was also observed in stable trauma patients after transfusion with 1 RBC unit, with the decrease in nitrite occurring after transfusion with RBCs stored for >25 days, but not with younger RBCs. Collectively, these data suggest that increased rates of reactions between intact RBCs and NO and nitrite may contribute to mechanisms that lead to storage-lesion-related transfusion risk. **[Biochem J. 2012;446:499-508]** PMID: 22720637

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INVOLVEMENT OF MEMBRANE TUBULIN IN ERYTHROCYTE DEFORMABILITY AND BLOOD PRESSURE

Amaiden MR, Monesterolo NE, Santander VS, Campetelli AN, Arce CA, Pie J, Hope SI, Vatta MS, Casale CH.[1]

Abstract

To test the hypothesis that erythrocyte deformability is influenced by changes in the content of membrane tubulin (Mem-tub).

Human erythrocytes contain tubulin distributed in three pools (membrane, sedimentable, soluble). Erythrocytes from hypertensive humans have a higher proportion of Mem-tub. Increased Mem-tub content in hypertensive patients was correlated with decreased erythrocyte deformability. Treatment of erythrocytes from normotensive individuals with taxol increased Mem-tub content and reduced deformability, whereas treatment of hypertensive patients erythrocytes with nocodazole had the opposite effect. In-vivo experiments with rats were performed to examine the possible relationship between Mem-tub content, erythrocyte deformability, and blood pressure. Spontaneously hypertensive rats (SHRs) showed lower erythrocyte deformability than normotensive Wistar rats. During the development of hypertension in SHR, tubulin in erythrocytes is translocated to the membrane, and this process is correlated with decreased deformability. In-vivo treatment (intraperitoneal injection) of SHR with nocodazole decreased Mem-tub content, increased erythrocyte deformability, and decreased blood pressure, whereas treatment of Wistar rats with taxol had the opposite effects.

These findings indicate that increased Mem-tub content contributes to reduced erythrocyte deformability in hypertensive animals. **[J Hypertens. 2012; 30: 1414-22]** PMID: 22525204

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ASSOCIATION OF PROTHROMBOTIC STATUS WITH MARKERS OF CEREBRAL SMALL VESSEL DISEASE IN ELDERLY HYPERTENSIVE PATIENTS

Nagai M, Hoshide S, Kario K.[1]

Abstract

Background-Aging and hypertension are well-known risk factors for cerebral white matter lesions. Prothrombotic status has been shown to be a risk factor for cardiovascular disease. In this study, we investigated the relationships among prothrombotic status, ambulatory blood pressure (ABP), and white matter hyperintensity (WMH) in elderly hypertensives. MethodsMeasurement of prothrombin fragments 1+2 (F1+2), von Willebrand Factor (vWF) and plasminogen activator inhibitor-1 (PAI-1), ABP monitoring (ABPM), and brain magnetic resonance imaging (MRI) were performed in 514 Japanese elderly hypertensives (72.3 years old, male 37%). WMH cases were further divided into deep subcortical white matter lesion (DWML) or periventricular hyperintensity (PVH).

Results-Deep WMH (DWMH) had significant positive correlations with age, use of antiplatelet agents, log F1+2, log vWF, log PAI-1, and 24-h systolic BP (SBP). PVH had significant positive correlations with age, male gender, smoking, use of antiplatelet agents, white coat hypertension (WCH), log vWF, and 24-h SBP. Severe PVH had significant positive correlations with age, use of antiplatelet agents, WCH, and 24-h SBP, and that was marginally correlated with log F1+2. In the logistic linear regression analysis, log F1+2 was significantly associated with DWMH ($P < 0.01$) and severe PVH ($P < 0.05$) adjusted for age and 24-h SBP. Log PAI-1 was significantly associated with DWMH ($P < 0.05$) adjusted for age and 24-h SBP.

Conclusions- In the present study, F1+2 and PAI-1 were positively associated with WMH after adjustment for 24-h SBP in elderly hypertensives. In addition to the conventional risk factors, prothrombotic status might serve as a significant determinant for WMH. **[Am J Hypertens. 2012;25: 1088-94]** PMID: 22739806

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THE DILEMMA OF INHERITED DYSFIBRINOGENEMIA DURING PREGNANCY

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Inherited dysfibrinogenemia is a rare disorder caused by mutations in the fibrinogen gene, described in approximately 400 families to date. We present the case of a 20-year-old woman at 7 weeks of pregnancy with a history of two first-trimester spontaneous abortions and a family history of thrombotic events. Her testing revealed evidence of dysfibrinogenemia, necessitating multidisciplinary management planning including Hematology, OB-GYN, Maternal-Fetal Medicine, Blood Bank Services and Anesthesia. Antenatal care included a combination of intravenous fibrinogen infusions to maintain fibrinogen levels above 100 mg/dl and anticoagulation with low molecular weight heparin. She had an uneventful full-term delivery and continued fibrinogen infusions and thromboprophylaxis for 6 weeks postpartum. The combination of fibrinogen infusions and anticoagulation maintained the balance between bleeding and clotting in our patient during pregnancy. We recommend a multidisciplinary team approach for the management of dysfibrinogenemia during pregnancy to provide successful pregnancy outcomes. **[Blood Coagul Fibrinolysis. 2012; 23:775-7]** PMID: 23135383

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PREDICTION OF PROGRESSION OF CORONARY ARTERY DISEASE AND CLINICAL OUTCOMES USING VASCULAR PROFILING OF ENDOTHELIAL SHEAR STRESS AND ARTERIAL PLAQUE CHARACTERISTICS: THE PREDICTION STUDY

Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, Takahashi A, Katsuki T, Nakamura S, Namiki A, Hirohata A, Matsumura T, Yamazaki S, Yokoi H, Tanaka S, Otsuji S, Yoshimachi F, Honye J, Harwood D, Reitman M, Coskun AU, Papafaklis MI, Feldman CL.1

Abstract

Background – Atherosclerotic plaques progress in a highly individual manner. The purposes of the PREDICTION Study were to determine the role of local hemodynamic and vascular characteristics in coronary plaque progression and to relate plaque changes to clinical events.

Methods – Vascular profiling (VP), using coronary angiography and intravascular ultrasound, was employed to reconstruct each artery and calculate endothelial shear stress (ESS) and plaque/remodeling characteristics in-vivo. Three-vessel VP (2.7 arteries per patient) was performed at baseline in 506 patients with acute coronary syndrome (ACS) treated with a percutaneous coronary intervention (PCI) and in a subset of 374 (74%) consecutive patients 6-10 months later to assess plaque natural history. Each reconstructed artery was divided into sequential 3-mm segments for serial analysis.

Results – One-year clinical follow-up was completed in 99.2%. Symptomatic clinical events were infrequent: only 1(0.2%) cardiac death; 4(0.8%) patients with new ACS in non-stented segments; 15(3.0%) patients hospitalized for stable angina. Increase in plaque area (primary endpoint) was predicted by baseline large plaque burden; decrease in lumen area (secondary endpoint) was independently predicted by baseline large plaque burden and low ESS. Large plaque size and low ESS independently predicted the exploratory endpoints of increased plaque burden and worsening of clinically relevant luminal obstructions treated with a PCI at follow-up. The combination of independent baseline predictors had a 41% positive- and 92% negative predictive value to predict progression of obstruction treated with a PCI.

Conclusions – Large plaque burden and low local ESS provide independent and additive prediction to identify plaques that develop progressive enlargement and lumen narrowing. CLINICAL TRIAL REGISTRATION INFORMATION: clinicaltrials.gov; Identifier: NCT01316159.

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