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The “morning cup of joe” as a modifiable factor in blood transfusion

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Precision medicine concepts can apply to red blood cell (RBC) transfusions, as follows: transfusing the right donor unit with the right quality into the right recipient in the right clinical setting at the right time to achieve an optimal outcome. Nonetheless, this requires a more nuanced definition of “RBC quality.” Thus, “storage quality” can be defined as the ability of RBCs to withstand the rigors of refrigerated storage, typically measured by storage hemolysis, 24-hour post-transfusion RBC recovery, and post-transfusion hemoglobin increment. In addition, “post-transfusion circulatory quality” can correspond to the long-term circulatory lifespan of the transfused RBCs, and their ability to perfuse and oxygenate tissues, which depend, for example, on RBC deformability and 2,3-biphosphoglycerate (2,3-BPG) levels, respectively.

RBC transfusion efficacy has improved dramatically over the last 100+ years. For example, ABO blood typing improved selection of donor/recipient pairs, thereby preventing virtually all acute hemolytic transfusion reactions (HTRs). Nonetheless, blood group alloimmunization still occurs, leading to delayed HTRs and difficulties in finding compatible units. In addition, improved anticoagulant and storage solutions, along with appropriate storage containers, allows for rapid RBC unit availability, efficient inventory management, and access to rare units. Identifying microbial pathogens transmitted by RBC transfusion, and developing relevant diagnostic tests, virtually eliminated transfusion-transmitted diseases, particularly in high-income countries, and pathogen-reduction technologies may soon solve this issue globally. Moreover, universal pre-storage leukoreduction (accompanied by irradiation) decreases HLA alloimmunization, febrile transfusion reactions, and transfusion-associated graft-versus-host disease. Finally, consensus statements and patient blood management approaches help optimize utilization of RBC transfusions and/or transfusion alternatives (e.g., pre-operative iron supplementation).

Given these advances, one could claim that no further improvements are necessary; nonetheless, issues remain. For example, we do not understand transfusion-related immunomodulation or the critical mechanisms underlying alloimmunization to RBC antigens; because of the latter, we still encounter highly-alloimmunized, chronically-transfused patients who become “untransfusable” because no compatible units are attainable. In addition, the “RBC storage lesion” worsens over time; thus, transfusing 42-day-old RBCs differs from 7-day-old RBCs, due to infusing potentially-damaging supernatant constituents (e.g., extracellular vesicles, mitochondrial DNA, non-transferrin-bound iron), providing less than an optimal dose (due to decreased post-transfusion RBC recovery), and providing RBCs with decreased deformability and 2,3-BPG (affecting perfusion and oxygen offloading, respectively). These issues can be partially rectified by “washing” or “rejuvenating” RBC units, but this increases cost and decreases the therapeutic dose.

Nonetheless, further improvements may not matter in certain scenarios, such as transfusing several units into a “transfusion-naïve” patient who is unlikely to ever be transfused again (e.g., an elderly male patient receiving a hip replacement), or when rapidly transfusing many units into a patient experiencing a massive, acute hemorrhage (e.g., in placenta accreta). However, in chronic transfusion settings (e.g., myelodysplastic syndrome, hemoglobinopathies), providing higher quality units could permit transfusion of 10-20% fewer units and/or fewer transfusion episodes, thereby improving quality of life (e.g., fewer missed days of school, work, or leisure), minimizing adverse outcomes (e.g., transfusion reactions, central line complications), and lessening iron overload. Moreover, high-quality RBCs may be important in particular high-risk situations (e.g., extremely premature neonates).[1]

One way to improve overall RBC transfusion quality is to enhance understanding of the RBC storage lesion and develop approaches to ameliorate it. To this end, current research leverages: mass spectrometry-enabled metabolomics, lipidomics, and proteomics; large epidemiological studies, including “vein-to-vein databases” (coupled with screening donors for RBC-relevant genetic polymorphisms); clinical trials with healthy volunteers and patients; and knockout and transgenic mouse models targeting RBC-relevant genes. These studies identified multiple factors affecting RBC transfusion quality (Table 1). Moreover, although mature RBCs, lacking virtually all organelles, are considered “simple,” these studies, in both normal and abnormal settings, discovered many more protein constituents and active metabolic pathways.[2] In addition, exposure to their environment dramatically affects RBC biology; indeed, their “exposome” includes microbiome products, pharmaceuticals (licit and illicit), diet (e.g., caffeine, vitamins, fatty acids), and the external environment (e.g., lead, smoking).[3]

In the current issue of Haematologica, Dzieciatkowska et al.[4] exploited these approaches to study whether caffeine modulates RBC storage quality and post-transfusion circulatory quality. Surprisingly, this psychoactive agent, widely consumed in coffee,[5] negatively affects RBC transfusion quality. Although coffee is often an inducement, or reward, for blood donation, and although it may help prevent donation-induced vasovagal reactions,[6] the current results, coupled with caffeine's short half-life *in vivo*, suggest that modifying its use could readily improve RBC transfusion quality.

The current paper[4] demonstrates that caffeine affects RBC physiology through extracellular and intracellular mechanisms (Figure 1). On the RBC surface, caffeine directly blocks adenosine receptor ADORA2b, thereby inhibiting signaling through AMP-activated protein kinase.[7] In addition, caffeine rapidly enters (and exits) RBCs by passive diffusion,[8] and binds to, and inhibits, glucose-6-phosphate dehydrogenase (G6PD), the rate-limiting enzyme of the pentose phosphate pathway (PPP).Thus, caffeine significantly affects the three major RBC pathways utilizing glucose: glycolysis (for ATP synthesis), the Luebering-Rapoport pathway (for 2,3-BPG synthesis), and the PPP (for synthesizing NADPH to ameliorate oxidative stress). Given the need to maintain energy levels during storage, RBCs redirect glucose metabolism towards ATP generation, thereby limiting 2,3-BPG and NADPH synthesis; caffeine exacerbates the latter, further compromising the RBC's ability to prevent damage from storage-induced oxidative stress (Figure 1).[9]

This paper[4] also identifies relevant gene-exposome interactions. For example, caffeine inhibits "wild-type" G6PD, but not the "common African" variant associated with G6PD-deficiency. Thus, caffeine does not additively or synergistically contribute to storage-induced oxidative stress of these G6PD-deficient RBCs, as might have been expected.[10] Therefore, elaborating the exact mechanism(s) by which caffeine inhibits G6PD activity is important.[11] In contrast, the negative effects of certain human *ADORA2b* polymorphisms on RBC storage quality, as with the *ADORA2b*-knockout mouse, are exacerbated by caffeine's effects on (wild-type) G6PD enzyme activity. Finally, given that hepatic CYP2A6 metabolizes caffeine, its genetic polymorphisms affect caffeine clearance from plasma and, consequently, from RBCs. The need for liver-dependent caffeine metabolism also explains why caffeine levels do not decrease during RBC storage.

Finally, given plasma caffeine's rapid metabolism (i.e., $t_{1/2}$ = ~5 hours) and its rapid equilibration with RBCs, short-term abstinence would dramatically decrease RBC concentrations, which could be beneficial for donated RBCs (if donors would comply!). However, it is currently unknown whether there is permanent structural damage to circulating RBCs[12] from any additional oxidative stress RBCs may experience due to caffeine exposure, which may be maintained throughout storage; this also merits further study.

In summary, one can now think of caffeine as an extensively-studied avatar of the RBC exposome. In addition, caffeine, which interacts with several polymorphic human genes (e.g., *ADORA2b*, *G6PD*, *CYP2A6*), can be considered as a modifiable factor that could improve the clinical practice of precision transfusion medicine.

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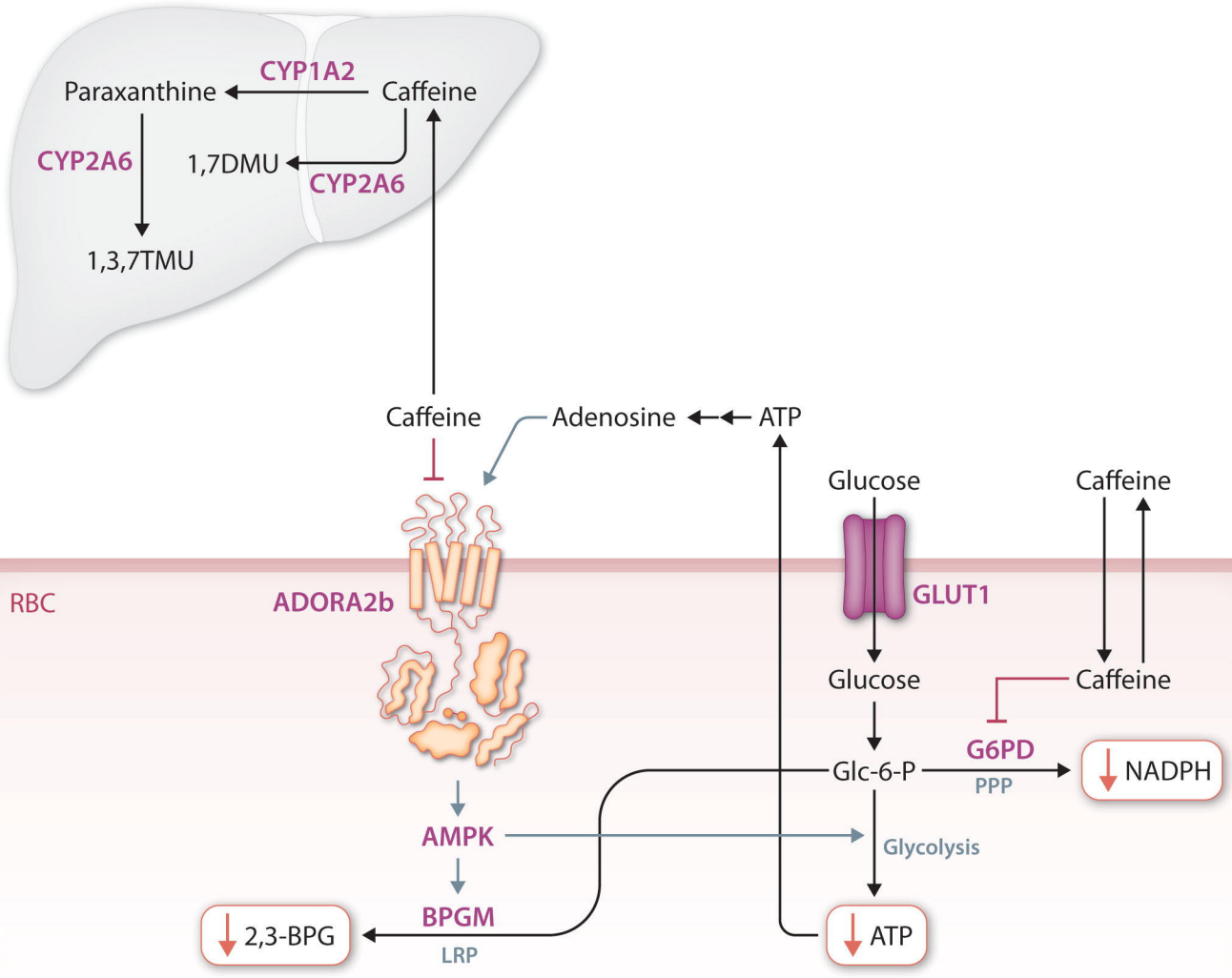
Table 1. Examples of factors affecting RBC storage quality

Factor	Effect on hemoglobin increment	Reference
Pre-storage leukoreduction of donor unit	Decrease	13
Irradiation of donor unit	Decrease	13
Donor G6PD deficiency	Decrease	10, 13
Storage duration of donated unit	Decrease	13
Male donor & female recipient	Increase	13
Donor caffeine consumption	Decrease	4

Figure 1. RBC metabolic pathways affected by caffeine exposure.

Legend: Schematic diagram indicating that caffeine is both a competitive inhibitor of adenosine binding to the ADORA2b adenosine receptor, which downregulates subsequent downstream signaling through AMPK, and is also a direct inhibitor of G6PD, the rate-limiting enzyme in the PPP. Taken together, this demonstrates that caffeine negatively affects the three major RBC pathways that utilize glucose (i.e., glycolysis, the LRP, and the PPP), thereby inhibiting their synthetic capacities (downward facing red arrows) to generate energy (i.e., ATP), enhance oxygen offloading by hemoglobin (i.e., 2,3-BPG); and resist storage-induced oxidative stress (i.e., NADPH); respectively. Abbreviations: ADORA2b: an adenosine receptor; AMPK: AMP-activated protein kinase; BPGM: biphosphoglycerate mutase; 1,7DMU: 1,7-dimethyluric acid; 1,3,7TMU: 1,3,7-trimethyluric acid; CYP1A2 and CYP2A6: two cytochrome p450 isoforms; LRP: Luebering-Rapoport Pathway; GLUT1: Glucose transporter 1; Glc-6-P: glucose-6-phosphate; G6PD: glucose-6-phosphate dehydrogenase; PPP: pentose phosphate pathway


CYP1A2
Paraxanthine
Caffeine
CYP2A6
1,7DMU
CYP2A6
1,3,7TMU
Caffeine
Adenosine
ATP
Glucose
Caffeine
RBC
ADORA2b
GLUT1
Glucose
Caffeine
G6PD
Glc-6-P
PPP
NADPH
AMPK
Glycolysis
BPGM
2,3-BPG
LRP
ATP