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Noninferior Red Cell Concentrate Quality after Repeated Air Rescue Mission Transport for Prehospital Transfusion

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Keywords

Prehospital transfusion · Red blood cell morphology · Air rescue · Red cell concentrate storage · Flow morphometry · Emergency transfusion

Abstract

Background: Transfusion of red cell concentrates (RCCs) is an integral therapy after severe hemorrhage or trauma. Prehospital transfusion offers an immediate intervention in emergency cases. Air ambulance-based prehospital transfusion, already used in different countries, is currently established in Germany. Limited information is available for regulatory-compliant transport logistics of RCCs and their quality after repeated air rescue missions. Thus, the aim of this study was (i) to validate regulatory-compliant logistics and (ii) to assess product quality, analyzing biochemical parameters and RBC morphology. ***Study Design and Methods:*** Due to regulatory requirements, we adapted a rotation system of 1 day transport, 1 day quarantine storage and 1 day storage over the entire RCC shelf life. RCCs transported on air rescue missions (flight group) were compared against a control group, treated identically except for helicopter transport. RCCs were visually inspected, and their temperature was documented throughout the entire rotation cycles. RCCs at the end of shelf life (end point samples) were assessed for levels of hemoglobin, hematocrit, free hemoglobin, hemolysis, mean corpuscular volume, potassium and pH. In addition, morphological changes were assessed using flow morphometry. ***Results:*** In total 81 RCCs were assessed in the flight group and 50 in the control group. Within the flight group, 30 RCCs were transfused. RCCs were dispatched on average 11 times (7–13 times). The average flight time was 18.3 h (6.6–28.8 h). The rotation system ensured adherence to regulatory guidelines, especially compliance to storage conditions of +2 to +6°C of intermediate storage. Biochemical and morphological quality parameters did not exhibit any changes upon repeated air rescue missions. A correlation with respect to the flight time was not observed either. ***Discussion:*** The quality of RCCs after repeated air rescue missions is noninferior to control samples regarding biochemical and morphological parameters. The product quality is within German regulations for up to 42 days of storage. The logistics and maintenance of the thermal conditions are safe and feasible. Thus, a rotation system of RCCs offers a regulatory-compliant option to supply air rescue missions with RCCs to allow life-saving prehospital transfusions at the incident scene.

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Introduction

Hemorrhage is one of the most common causes of death after trauma [1–3]. Transfusion of blood components in hemorrhagic shock is an integral part of therapy in the hospital [4, 5]. Integrating clinical transfusion therapy already into prehospital care of severely injured patients was first implemented in the military [6] and recently also in the civilian sector in a few European and non-European countries [7–9]. Benefits of preclinical transfusions have been documented especially when patients need to be transported long distances [10–13]. Short transport distances are currently under investigation in certain countries [7, 11, 14].

For prehospital transfusion various aspects need to be taken into account: severity of trauma, high risk for hemorrhagic shock, urgency of immediate transfusion and limited availability of blood products [4]. Air ambulance appears particularly useful as it allows for long ranges and fast transport times. In order to implement air ambulance-based transport for prehospital transfusions in Germany, the requirements of the Transfusion Act, the Hemotherapy Guidelines and the Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives of the Bundesärztekammer have to be followed [15, 16]. In particular, the specifications for transport and storage of red blood cell concentrates (RCCs) are crucial. Limited information is available for transport logistics of RCCs especially regarding repeated transport, total flight hours and reentry into regular blood bank storage and use. Current German pilot projects established a concept transporting RCCs for up to 3 days and reentering into regular blood bank storage and use [17, 18]. Due to regulatory requirements, we adapted a rotation system of 1 day transport, 1 day quarantine storage and 1 day storage over the entire RCC shelf life.

Previous studies already suggested that helicopter transport (e.g., large temperature fluctuations, changes in air pressure and vibrations) did not affect RCC quality compared to control groups [17, 19]. However, detailed analyses of RCC quality after repeated transport throughout the shelf life of blood components with different flight times are lacking. The aim of this study was (i) to establish a procedure complying to regulatory requirements regarding the logistics, packaging, transport, and storage of RCCs and (ii) to assess product quality, analyzing biochemical parameters and RBC morphology using our newly developed flow morphometry method [20]. To achieve this, RCCs transported on air rescue missions (flight group) were compared against a control group, treated identically except for the transport.

Materials and Methods

Storage and Transport Logistics

To provide patients suffering from vital threatening hemorrhage with blood components at an early stage, a system was implemented and validated which ensures transport and storage of RCCs to the flight center (DRF Luftrettung GmbH) and back to the blood bank of the Mannheim institute of the German Red Cross Blood Services (blood bank) on a daily routine basis. Due to regulatory requirements, a rotation system was established where RCCs as well as lyoplasma were transported every third day (Fig. 1). Every day, 2 RCCs with 2 lyoplasma units, 3 bedside tests, and a temperature data logger (ThermoScan Datenlogger™, TRANSMED, Nürnbrecht, Germany) were packed in a passively cooled Pelican Crēdo ProMed™ 4-L carry bag shipper (PELI Biothermal™, Plymouth, MN, USA) (suppl. Fig. 1; see www.karger.com/doi/10.1159/000520650 for all online suppl. material). These shippers are tested to ISTA7D profiles, as stated by the company. Before adding the blood products, the Crēdo box was equipped with coolants filled with phase change material and vacuum-insulated panels to assure a temperature range of +2 to +6°C (day 1). The cool box was transported to the DRF station and taken on each mission of the DRF rescue helicopter (Airbus EC 135 helicopter, Christoph 53 of the DRF Stiftung Luftrettung, base Mannheim). At the end of the mission day, the products were returned back from the DRF station to the blood bank in exchange for the next products packed within a Crēdo box (day 2). After return, the products underwent a first visual inspection, and their temperature was documented. The allowed transport temperature range is defined as +2 to +10°C. Regulatory specifications, however, require adherence to storage conditions, defined as +2 to +6°C (Guideline Hemotherapy Federal Medical Association [15]). After 1 day quarantine storage, defined release criteria were checked: visual inspection, compliance of temperature range and shelf life (day 3). Upon proof of compliance, the products reentered the rotation cycle. This process was repeated until emergency use of the blood components or until the end of the shelf life of the RCCs. The control samples were packed and unpacked in the same way as the flight samples. However, instead of being transported to the DRF station, the control samples were stored for the same time duration as the flight samples in Crēdo shippers, which were held at room temperature within the blood bank.

Operating times of the helicopter were from sunrise (7:00 a.m. at the earliest) to sunset. During this time, the products were carried on regular missions. Flight altitude was around 300 m. Flight time durations were documented for each RCC and total flight duration added up at the end of shelf life.

Rotation System and Sampling

From both control and flight RCCs, end point samples were taken (a) once the RCC reached the end of their shelf life or (b) after transfusion or (c) after not passing the compliance check according to visual inspection or temperature range (Fig. 1). For some units, initial samples were taken. Before sampling, the units were always rotated for 20 min at 0.1 rps (ACR Rotator, Lmb Technologie GmbH, Schwaig, Germany) and then samples taken from sterile welded off pouches or segments.

Biochemical Quality Control

End point samples (flight and control group) were assessed for levels of hemoglobin (Hb), hematocrit (Hct), free hemoglobin (fHb), hemolysis, mean corpuscular volume (MCV), potassium, and pH.

Hb, Hct, and MCV were measured from a 4-mL aliquot using a hematology analyzer (CELLDYN Ruby, Abbott GmbH & Co. KG, Wiesbaden, Germany). Potassium levels and pH values were measured using a blood gas analyzer (ABL 80 Flex, Radiometer

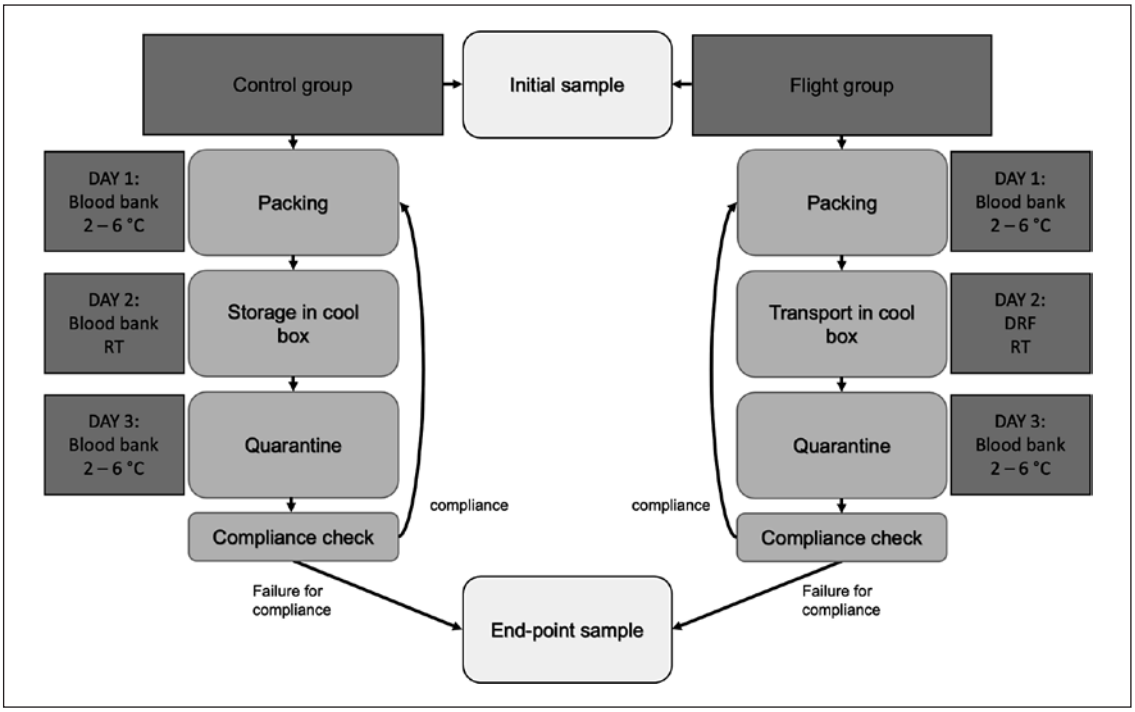

Fig. 1. Flow diagram of the rotation system for the RCC logistics. Dark gray indicates location, timing, and temperature while gray background indicates the steps of the rotation cycle. Light gray boxes indicate sampling.

GmbH, Krefeld, Germany). For the fHb measurement, 2-mL aliquots were centrifuged at 4,000 rpm for 10 min (Rotina 38, Hettich GmbH & Co. KG, Tuttlingen, Germany). 50 µL of the supernatant were diluted in 500 µL buffer solution (fHb, Bioanalytic GmbH, Freiburg, Germany) and analyzed photometrically (DR 5000, Hach Lange GmbH, Düsseldorf, Germany). Hemolysis levels were calculated (equation 1):

$$\text{hemolysis}\,(\%) = \frac{\left(100 - \text{Hkt}\left[l/l\right]100\ \left[\%\right]\right)\text{fHb}\left[g/l\right]}{\text{Hb}\left[g/\text{dl}\right]10}.$$

Flow Morphometry

During storage, RBCs undergo progressive biochemical and morphological changes collectively termed as storage lesions. Healthy discocytes degrade via the echinocyte pathway and finally undergo apoptosis [21, 22]. During this process, the cells experience an expansion of the outer leaflet relative to the inner leaflet of their cell membrane [23] changing from discoid to spiculated echinocyte and finally into spherical morphologies [24] (Fig. 2). These spherical morphologies, spheroechinocytes and spherocytes, are less effective in oxygen delivery after transfusion [25]. Previous work showed a correlation between the proportion of spherical forms and hemolysis [20].

For flow morphometry, a 100-µL sample was diluted 1:400 in 0.9% NaCl. Erythrocytes were incubated for 10 min at room temperature before measurement to stabilize their shapes. Analysis was performed as published previously using a flow cell system (Ibidi GmbH, Martinsried, Germany) combined with an in situ suspension microscope [26, 27]. Approximately 3,000 microscopic images of erythrocytes were captured within the moving suspension of each sample. The detected sharp cells were classified using a convolutional neural network (Resnet50), which divides the RBCs into 6 classes representing different degrees of degradation (Fig. 2). Additionally, we calculated a morphological index (MI) to receive a single value for the quality of each RCC. The weighted values for the different morphologies were slightly modified as compared to the conventional definition of the MI [28]. This was done in order to align with our morphology classification: discocytes (weighted value 1), echinocytes1 (weighted value 0.8), echinocytes2 (weighted value 0.6), echinocytes3 (weighted value 0.4), and the spherical forms (weighted value 0.2).

As for the biochemical quality control, end point flow morphometry measurements were performed comparing flight to control samples. In addition, change rates of morphologies were calculated comparing initial and end point samples.

Statistics

Statistical analysis was performed using GraphPad Prism 9.1.2 (GraphPad Software, San Diego, CA, USA). Data are depicted as scatter plots with mean value and 95% confidence intervals (95% CI). Flight and control groups were compared using unpaired two-sided Mann-Whitney U tests. A p value of 0.05 was regarded as statistically significant ($\alpha = 0.05$). Possible effect sizes of the flight are plotted as Hodges-Lehmann estimates (medians of the computed difference between each value in the flight group and each value in the control group) with 95% CIs.

Simple linear regression was used to calculate the correlation between flight time duration and RBC quality parameters. The linear regression coefficient was used as a measure for goodness of fit in combination with p value for the slope´s difference to nonzero.

Results

A rotation system allows regulatory-compliant storage and transport logistics of RCC units for air rescue missions.

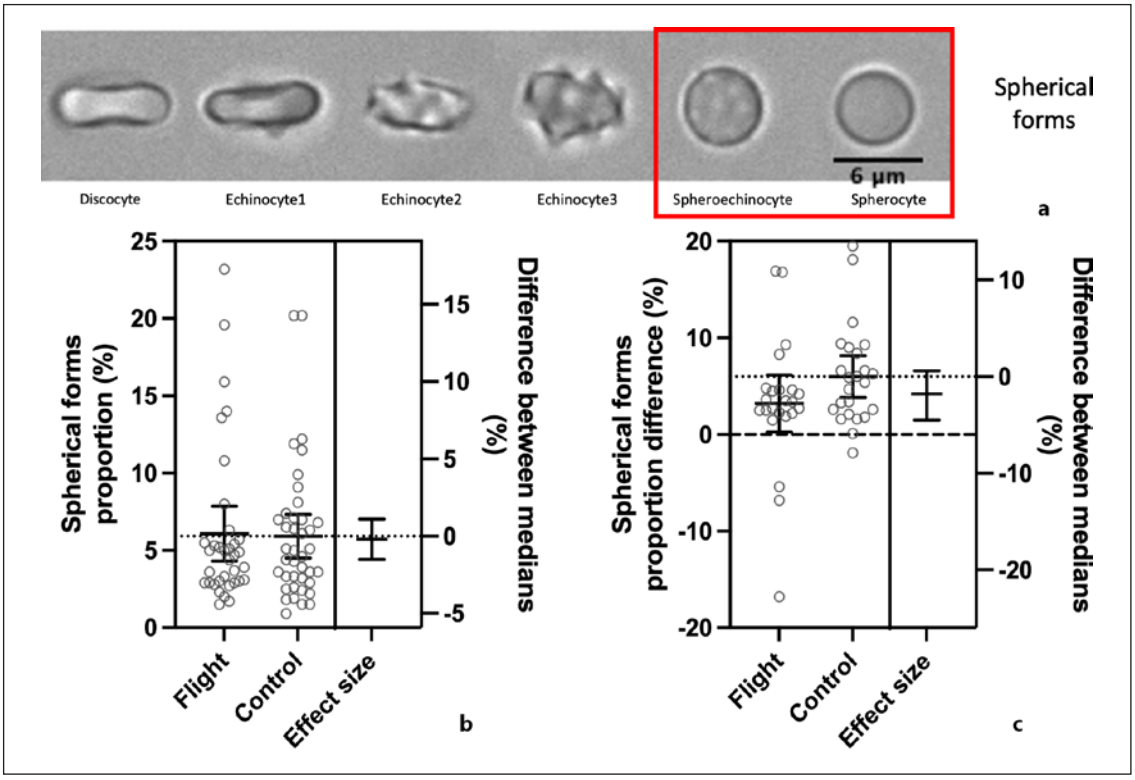

Fig. 2. Flow morphometry of spherical RBCs. **a** The CNN classifies RBCs into the classes represented by the cell portraits: discocytes, echinocytes1, echinocytes2, echinocytes3, spheroechinocytes and spherocytes. **b** The proportion of spherical forms in percent (end point measurement; flight $n = 35$, control $n = 40$). **c** The change of that proportion between the initial and end point measurement of each RCC (change rate; flight $n = 23$, control $n = 24$). The sample groups are depicted as scatter plots with mean value and 95% CI. **b** and **c** both depict a second y-axis, which indicates the Hodges-Lehmann estimates of flight and control group (effect size). The effect size of the proportion of spherical forms caused by flights is measured as −0.2% with a p value of 0.766 and 95% CI ranging from −1.5 to 1.1%. The effect size of the proportion of the change rates of spherical forms between initial and end point measurements is −1.8% with a p value of 0.151 and 95% CI from −4.5 to 0.6%.

In total 81 blood group 0 rhesus D-negative RCCs were included in the flight group and 50 blood group AB rhesus D-positive RCCs in the control group. RCCs were dispatched on average 11 times (7–13 times) before they were excluded from the study (Fig. 3). The average flight time duration was 18.3 h (6.6–28.8 h).

The rotation system ensured adherence to regulatory guidelines, especially to defined transport temperature ranges. The project ran over an entire period of 12 months, thus encompassing all seasonal temperature ranges. Only 4 from in total 131 RCCs showed temperature deviation issues, 2 within each study group. We excluded 3 units from the study upon visual inspection – the suspicion of hemolysis, however, was not confirmed. The established rotation system was feasible, allowing for packaging, transport, and storage of RCC units with quality assurance in between the cycles.

Within the flight group, 30 RCCs were transfused [29].

Biochemical Parameters of RBC Quality Show Noninferiority of RCCs after Repeated Air Rescue Missions

The next step was to test whether repeated air rescue missions might affect quality attributes of RBCs. The German hemotherapy guidelines ask to document the intactness of RCC bags, and no hemolysis upon visual inspection and a hemolysis rate below 0.8% at the end of shelf life. All units were intact and had a hemolysis rate below the limit of 0.8%. There were no significant differences between flight and control samples with respect to any biochemical measurement (Fig. 4).

Flow Morphometric Analysis Supports Noninferiority of RCCs after Repeated Air Rescue Missions

Flow morphometry measurement combined with a convolutional neural network (Resnet50) analysis enabled us to classify the RBCs into 6 classes representing different degradation stages (Fig. 2). The spherical forms with reduced oxygen transport capacity are indicated in red [25] (Fig. 2a). Flight and control group showed no difference between the

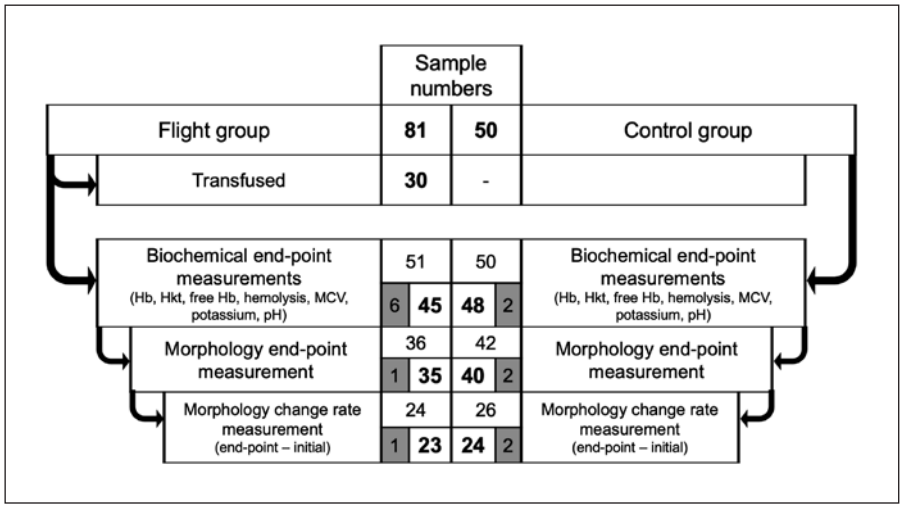

Fig. 3. RCC subgroups in flight and control groups depicted separately with respect to different quality control measurements. Bold numbers indicate the number of RCCs included in the study and in analysis. Gray fields indicate the number of samples excluded from analysis due to temperature deviation or failure of visual inspection. Only samples stored longer than 30 days were analyzed.

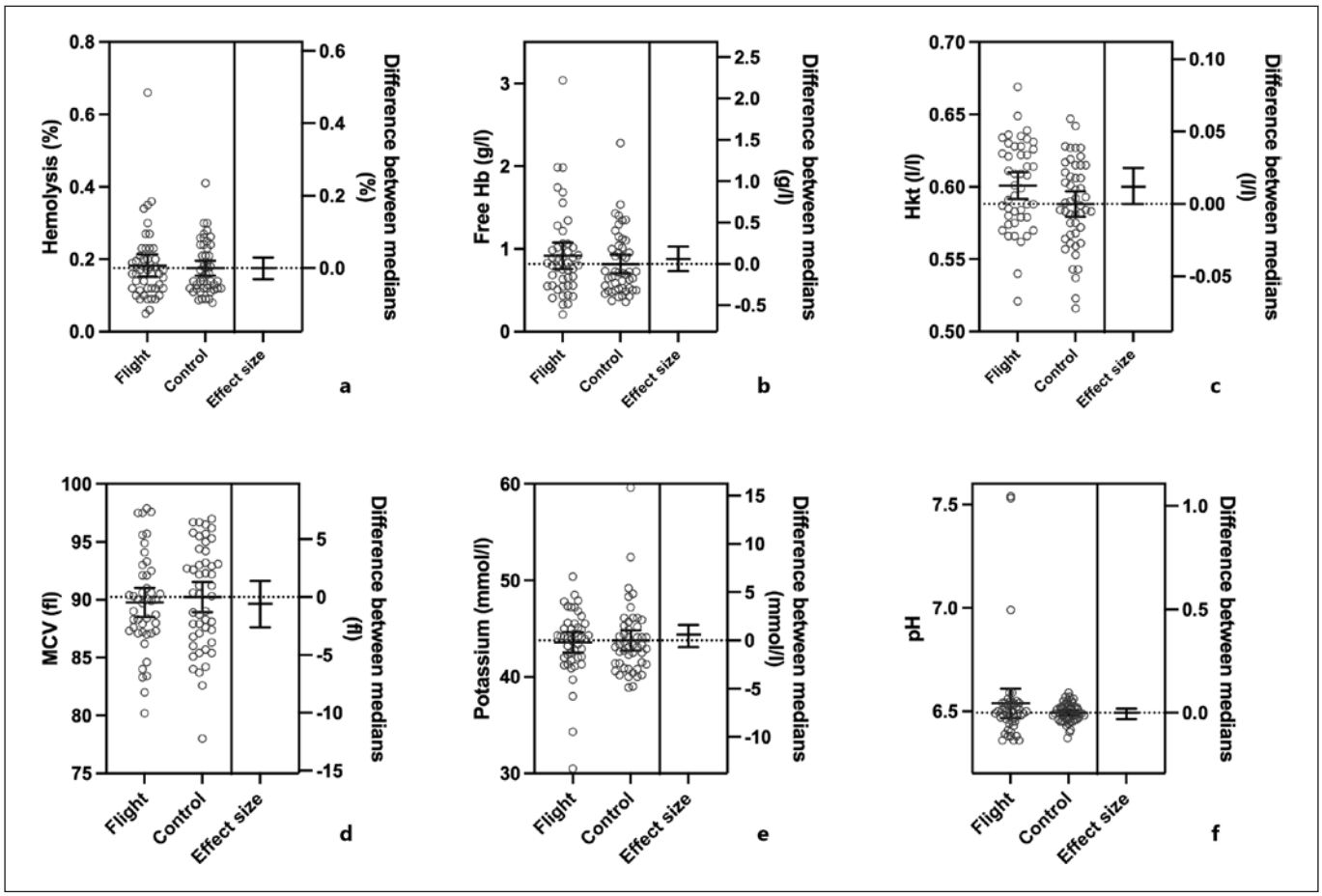

Fig. 4. Biochemical parameters of RCCs in flight and control groups. The measured biochemical variables are depicted on the left *y*-axis, the Hodges-Lehmann estimate on the right *y*-axis. The sample groups ($n = 45$ flight and $n = 48$ control group) are depicted as scatter plot with mean values and confidence intervals (95% CI). The Hodges-Lehmann estimate with the requested range of the 95% CI displays the possible effect size of the flight. The effect sizes of the biochemical parameters with corresponding p values and 95% CI are shown. **a** Hemolysis: 0.0% ($p = 0.962$, 95% CI = −0.03 to 0.03). **b** Free hemoglobin: 0.059 g/L ($p = 0.396$, CI = −0.088 to 0.209). **c** Hematocrit: 0.012 L/L ($p = 0.053$, CI = 0.0–0.025). **d** Mean corpuscular volume (MCV): −0.6 fL ($p = 0.542$, CI = −2.6 to 1.4). **e** Potassium: 0.6 mmol/L ($p = 0.396$, CI = −0.7 to 1.6). **f** pH: 0.0 ($p = 0.983$, CI = −0.03 to 0.02).

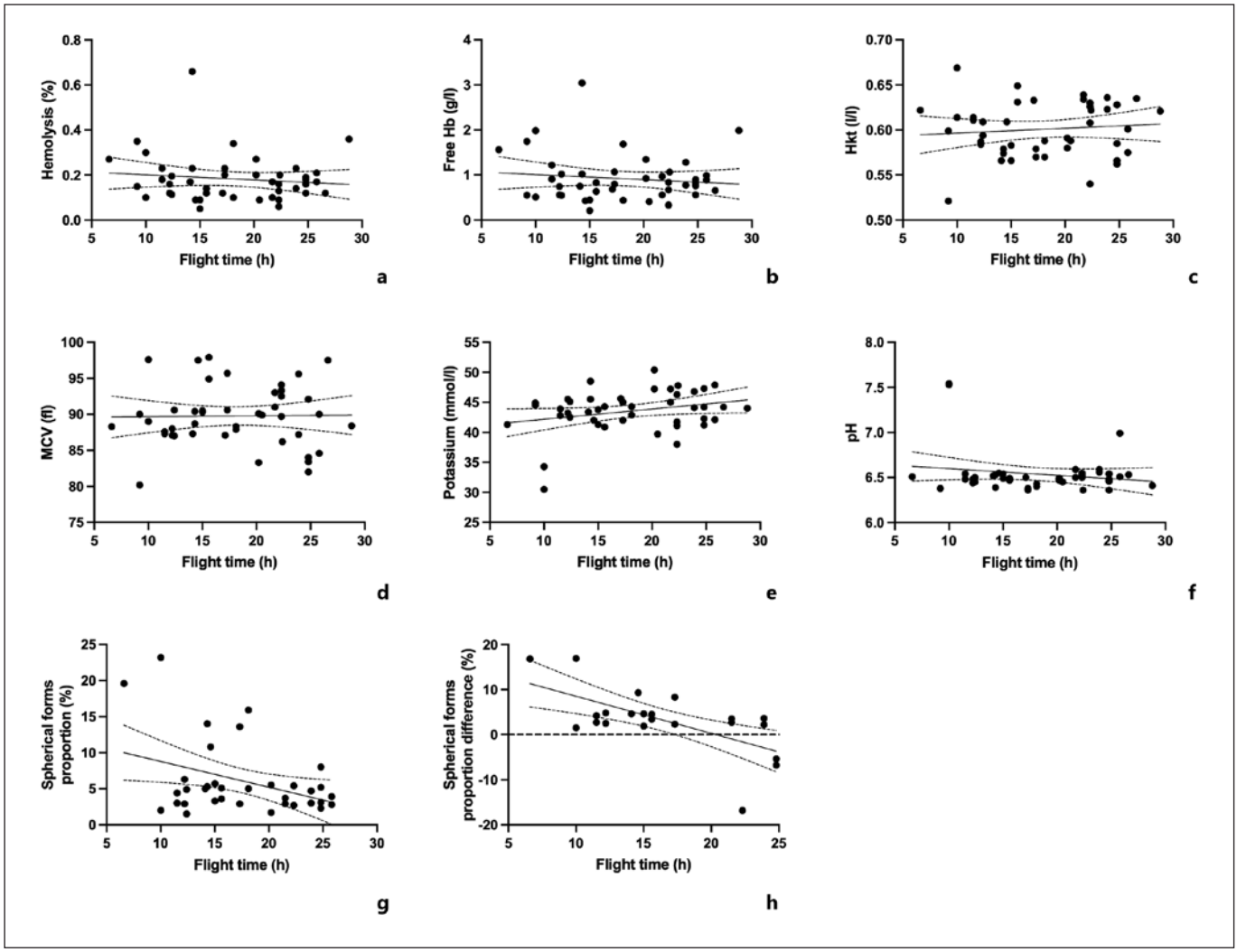

Fig. 5. Correlation between flight time duration and RBC quality attributes. Biochemical (**a–f**, $n = 45$) and morphological (**g**, $n = 35$; **h**, $n = 23$) parameters plotted versus flight time duration. The straight lines represent linear regression fits. The dashed curved lines represent the confidence bands of the fitted line. The slopes of the straight lines together with regression coefficients and p values for this slope´s difference to nonzero are shown. **a** Hemolysis: −0.002, $R^2 = 0.003$ ($p = 0.42$). **b** Free hemoglobin: −0.011, $R^2 = 0.014$ ($p = 0.43$). **c** Hematocrit: 0.001, $R^2 = 0.010$ ($p = 0.51$). **d** Mean corpuscular volume (MCV): 0.012, $R^2 = 0.0$ ($p = 0.92$). **e** Potassium: 0.171, $R^2 = 0.079$ ($p = 0.06$). **f** pH: −0.007, $R^2 = 0.032$ ($p = 0.24$). **g** Spherical forms proportion: −0.357, $R^2 = 0.141$ ($p = 0.03$). **h** Spherical forms proportion difference (aging effect): −0.823, $R^2 = 0.407$ ($p = 0.00$).

percentages of spherical forms (Fig. 2b). Comparing initial and end point samples by calculating the change rate (i.e., their aging), likewise no significant differences were apparent. Besides the percentage of spherical forms in the RCCs we also calculated the MI (suppl. Fig. 2). It displays no significant differences between the two groups. We further verified that the mode of sampling from routine RCCs did not affect our measurement by comparing pouch and segments which yielded comparable results (suppl. Fig. 3).

RBC Quality Attributes Were Not Affected by the Flight Time Duration

Given the results above, the data documented the noninferiority of RBC quality attributes after repeated air rescue missions related to the total flight time duration. By using simple linear regression models, the correlation between quality attributes and total flight time duration was calculated (Fig. 5a–h). This evaluation clearly indicates that flight time duration does not correlate with any of the biochemical and morphological parameters.

Discussion/Conclusion

To ensure regulatory-compliant storage and transport logistics of RCCs for emergency air rescue missions, we (i) established a rotation system for RCCs for repeated air rescue missions and (ii) verified the nonin-

ferior quality of RCCs after repeated air rescue transportation.

Optimized transport and storage logistics were achieved by implementing a rotation system based on a passive cooling box [30, 31], which assured maintenance of the required temperature over the entire process. Only 4 out of 131 units showed minor temperature deviation exceeding the allowed range during storage of +2 to +6°C.

We considered 4 factors to be of biggest impact on the RCCs' quality during the air rescue transport: (i) the temperature, (ii) the repeated packing process, (iii) the helicopter vibration, and (iv) the lower air pressure related to flight height. Decreased and increased temperature may compromise the product quality [32, 33]. Our data indicate that none of these factors affected RCC quality. Furthermore, red blood cells in vivo are used to being squeezed and pushed extensively within the vascular system. This mechanical stress is far greater than the moderate stress caused by the vibration of the helicopter. The change in air pressure during different flight heights has been shown to affect RBC quality during long-distance flights at 2,000 m altitude [34]. Yet in this study, the air rescue helicopter flight altitude was around 300 m and was without effect [17]. Indeed, our comprehensive quality data show no deterioration of RBCs. With respect to all investigated RCC quality attributes no significant differences between flight and control group were found. Furthermore, the RCC quality attributes were not affected by the total cumulated flight time duration.

The hemolysis level, set to a maximum of 0.8% at the end of shelf life, is the only biochemical quality parameter defined within the specifications of the German hemotherapy guideline [15]. Previous studies already indicated that the hemolysis rate is not increased after air rescue missions [17, 19]. We furthermore show that the average hemolysis rate for the flight RCCs (0.18%) and control RCCs (0.18%) were below the average (0.55%) of hemolysis commonly obtained after 42 days of storage [35]. Considering the necessity to document noninferior quality by additional parameters [36], we assessed further biochemical as well as morphological parameters, all of which are closely related to storage lesion [21, 22, 37]. Despite the large variety of different RBC quality attributes measured, no difference between the flight group and the control group became apparent, indicating noninferior quality of RCCs after repeated air rescue missions. Likewise, no correlation with respect to the flight time duration (6.6–28.8 h with 7–13 missions) was observed.

We conclude that the quality of RCCs after repeated air rescue missions is noninferior to control samples regarding biochemical and morphological parameters during storage. Within German regulations, RCCs are allowed to be stored for 42 days within a temperature range of +2 to +6°C of intermediate storage. Compliance with this regulation can be ensured during the air rescue missions by organizing a suitable logistic based on a rotation system. By applying efficient cooling devices, the logistics and maintenance of the thermal conditions are safe and feasible. A well-defined rotation system for the use of RCCs in air rescue missions with routine check-ups provides a resource-saving option and enables the provision of RCCs in agreement with the German transfusion guidelines. This novel concept allows life-saving prehospital transfusions directly at the incident scene.

Acknowledgement

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Statement of Ethics

All blood donors have given their written informed consent. Blood transfusions were performed according to the hemotherapy guidelines and required no ethical approval.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material. Further enquiries can be directed to the corresponding author.

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