Proton resonance frequency thermometry to analyse red blood cell warm-up from 1°C to 10°C: appraisal of the '30 minutes rule in transfusion medicine'

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Purpose

Storage and transport of human red blood cell concentrate (RBC) is subject of a variety of laws and regulations whereas temperature is a key measure in RBC quality control. According to international guidelines, RBC should be stored at 1°C - 6°C and must not exceed 10°C during transport [1-3]. Once exceeded, units must be used or discharged. Definition of time RBC units can be exposed to ambient temperature without exceeding the recommended temperature limit of 10°C, commonly roughly estimated applying the "30 minute rule", challenges the investigation of the three-dimensional temperature distribution of RBC during warming.

Since thermal warming is not a spontaneous but complex multifactorial, three-dimensional process, previous studies applying thermocouple data loggers to investigate RBC warm up processes are mainly limited due to the invasive, one-dimensional nature of data acquisition, data-logger positioning and dimension, uncontrolled RBC unit geometry, ambient room temperature fluctuations as well as lack of repeatability of settings [5, 9-11]. Magnetic resonance (MR) thermometry represents a unique tool for non-invasive, contactless, three-dimensional assessment of thermal processes. Temperature monitoring is feasible with various temperature sensitive MR parameters. Proton resonance frequency (PRF) temperature mapping is the method of choice for fast, stable and accurate temperature measurements [17-19].

The purpose of the present study was to use PRF thermometry to measure the three-dimensional temperature distribution in RBC withdrawn from refrigerated storage (1°C - 6°C) and exposed to ambient temperature (21.25°C) to investigate the times when RBC surface, core and mean temperature exceed 10°C and if respective times correlate with each other to critically review the applicability of the "30-minutes rule" as appropriate estimate for RBC temperature not exceeding 10°C.

Methods and Materials

RBC sample collection

65 samples (12 units for calibration and 53 RBC units investigated by PRF thermometry) of outdated or unaccepted for transfusion re-suspended RBCs were used within the study. Whole blood donations were obtained according to the Austrian regulations for blood donation from healthy volunteer blood donors after informed written consent and collected into triple bags (LCR5 filtration set) containing 63 ml citrate phosphate dextrose (MacoPharma LAB, Pharmaceutiques, Tourcoing, France). After centrifugation at 4000·g for 10 min at 20°C, RBC and plasma were separated from buffy coat fraction and...
transferred into satellite containers using an automated separator (Compomat G4, NPBI, Amsterdam, Netherlands). Within 30 min after separation RBC was leukoreduced using the LCR5 leukoreduction filter (MacoPharma LAB, Pharmaceutiques, Tourcoing, France) and re-suspended in 100 ml of saline adenine glucose mannitol (SAGM containing 900 mg of glucose monohydrate, 877 mg of sodium chloride, 525 mg of mannitol and 16.9 mg of adenine).

**Proton resonance frequency coefficient of RBC**

RBC proton resonance frequency (PRF) thermal coefficient was derived from calibration measurements. A calibration unit (refer to Figure 1) build-up of RBC, a reference bulb thermometer (Ludwig Schneider Messtechnik, Germany, overall accuracy ± 0.2°C) and a reference phantom (5 g agar solved in 500 ml water) kept at ambient temperature to measure phase drifts was positioned in a 1.5T MR system (Siemens Magnetom Espree, Germany), centered in a 12 channel matrix head coil.

**Fig. 1**: Proton resonance frequency thermal coefficient measurement setup. 220 ml of refrigerated stored red blood cell concentrate (RBC) filled in a mountable plastic cup is positioned in the calibration unit (RBC-CU) adapted with an alcohol thermometer (T) and a reference phantom (RTI) kept at room temperature throughout experiments. The RP was placed in a plastic frame next to the RBC sample (A). For measurements the RBC-CU was positioned in the center of the matrix head coil (MHC) in the isocenter of the MRT system (B).

**References:** Department of Radiology, Medical University of Graz - Graz/AT

Measurements were performed using a 2D multislice gradient echo (GRE) sequence (TR = 33.15 ms, TE = 20 ms, flip angle = 14°, voxel size = 1.1×1.1×7.5 mm³, FoV = 170×170
cm², BW = 65 Hz/Pix, number of slices = 7, data acquisition time = 38 s) covering the thermometer tip with gapless transversal slices (refer to Figure 2). After acquisition of reference images, difference phase images and thermometer reference temperatures were measured with 3 min pause time for RBC temperatures between 1°C - 18°C.

Fig. 2: Proton resonance frequency thermal coefficient measurements. Sagittal TSE scout (A), coronal EPI magnitude (B) and phase (C) images showing red blood cell concentrate (RBC) and a reference phantom (RP). The slice containing the thermometer bulb was evaluated (indicated as yellow line) by drawing regions of interest in RBC (ROIR_BC) and the preference phantom (ROI_RP).

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RBC proton resonance frequency thermal coefficient analysis

Temperature induced phase shifts were obtained as differences between means of phase changes of RBC located around the thermometer tip during warm up and means of reference phantom phases. #RBC was determined for each calibration measurement series from linear fit of resultant phase differences # as function of temperature T between 1 and 18°C according to

$$\alpha_{RBC} = \frac{1}{2\pi \cdot \gamma \cdot B_0 \cdot TE} \frac{d\phi}{dT}$$

Table 1: [17]
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where \# is the gyromagnetic ratio of $^1$H nuclei, $B_0$ the main magnetic field strength and $d\#/dT$ the slope of the respective fit.

**RBC temperature mapping**

RBC temperature images were acquired with a 2D multislice gradient echo sequence (TR = 33.15 ms, TE = 20 ms, flip angle = 14°, voxel size = 1.1×1.1×7.5 mm$^3$, FoV = 170×170 cm$^2$, BW = 65 Hz/ Pixel, number of slices = 7, data acquisition time = 38 s) covering the entire RBC volume with equidistant slices (gap = 90%-95%) for a total investigation time of 69.7 min.

**RBC image analysis**

MR images were transformed to RBC temperature maps by dedicated software developed in Matlab (R2010b. The MathWorks Inc. Natick, Massachusetts) employing a PRF thermal coefficient of RBC derived from calibration measurements. RBC unit height, width ($w_{pouch}$) and center ($c_{RBC}$) were determined from the central slice (refer to Figure 3). Thermal RBC core ($RBC_{core}$) was defined as region with minimum temperature in the central slice throughout warm up. Its position was specified as relative distance from $c_{RBC}$. RBC mean temperature $T_{mean}$, associated with the thermal state of RBC after "gently mixing", was calculated as mean value of temperatures measured in the entire RBC volume at a specific time during warm up. As the excess of 10°C was studied, the following times were derived from temperature maps: $t_{mean}$ was the time when $T_{mean}$ exceeded 10°C, $t_{surface}$ the time when RBC volume started to exceed 10°C and $t_{core}$ was the time when 100% of RBC volume exceeded 10°C.
Fig. 3: RBC unit height (h), width (w_pouch) and geometric center (c_RBC) were determined from the central slice. Thermal RBC core (RBCcore) was defined as region with minimum temperature in the central slice throughout warm up. Its position was specified as relative distance from RBC pouch center c_RBC (A). Discrete time course of RBC volume fraction (rel vol_RBC) during warm up was interpolated by cubic splines (solid line). To circumvent noise effects, slope at half maximum was used to calculate the times tsurface and tcore when RBC volume starts to exceed 10°C and when 100% of RBC volume has exceeded 10°C, respectively (B).

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Images for this section:

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Results

**RBC proton resonance frequency thermal coefficient**

Linear correlation between RBC phase differences and temperature changes was close to perfect (mean correlation coefficient 0.999 ± 0.001). Mean PRF thermal coefficient of RBC derived as average of 12 calibration measurements was $#_{\text{RBC}} = 1.05 \times 10^{-8} \, ^\circ\text{C}^{-1} \pm 0.02 \times 10^{-8} \, ^\circ\text{C}^{-1}$.

**RBC warm up temperature distributions**

During warm up, heat was continuously transferred from RBC surface to the adjacent layers, causing a non-uniform temperature distribution in the sample with isotherms located symmetrically around $\text{RBC}_{\text{core}}$ in both transversal (horizontal and latitudinal) extensions of the sample. In vertical extension $\text{RBC}_{\text{core}}$ was displaced by 13% ± 4% form pouch center. Means of times when mean, surface and core temperatures exceed 10°C were 24 min ± 5 min, 16 min ± 4 min and 36 min ± 7 min, respectively (refer to Figure 4).
Fig. 4: Average times of 53 RBC samples investigated by PRF thermometry when mean, surface and core temperatures exceed 10°C.

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All times significantly depended on $T_{\text{storage}}$ and $w_{\text{pouch}}$ (refer to Figure 5). Dependence of times when mean, surface and core temperatures exceed 10°C on RBC volumes ($R^2 = 0.84, 0.81$ and $0.75$ for $t_{\text{mean}}$, $t_{\text{surface}}$ and $t_{\text{core}}$ respectively) was smaller than on $w_{\text{pouch}}$. 
Fig. 5: Scatter plot of measured times when RBC mean temperature (A) surface temperature (B) and RBC core (C) exceed 10°C depending on storage temperature T_storage of the respective RBC. Straight lines are fits derived from bilinear regression analysis for minimal, mean and maximal sample RBC pouch widths w_pouch.


Use of surface and core measurements for prediction

Times when mean, surface and core temperatures exceed 10°C strongly correlated with each other (refer to Figure 6). Slightly broader prediction bands of t_surface were related to a moderate dependence of residuals on w_pouch (r = 0.35 for correlation with t_mean and t_core). Mean temperatures at t_surface and t_core were T_mean(t_surface) = 8.1°C ± 0.4°C and T_mean(t_core) = 12.2°C ± 0.4°C. At both times T_mean correlated with T_storage (r = 0.61, p < 0.0001 for t_surface and r = -0.58, p < 0.0001 for t_core): Whereat T_mean(t_surface) increased with T_storage according to T_mean(t_surface) = 7.4 + 0.18×T_storage, T_mean(t_core) decreased with T_storage according to T_mean(t_core) = 12.8°C - 0.17×T_storage.
Fig. 6: Scatter plot and linear regression lines together with 95% prediction bands of tmean versus tsurface (A), tcore versus tsurface (B) and tmean versus tcore (C). Regression equations are understood with times in minutes, temperatures in °C and pouch width in cm.


Images for this section:

Fig. 4: Average times of 53 RBC samples investigated by PRF thermometry when mean, surface and core temperatures exceed 10°C.
**Fig. 5:** Scatter plot of measured times when RBC mean temperature (A) surface temperature (B) and RBC core (C) exceed 10°C depending on storage temperature $T_{\text{storage}}$ of the respective RBC. Straight lines are fits derived from bilinear regression analysis for minimal, mean and maximal sample RBC pouch widths $w_{\text{pouch}}$.

**Fig. 6:** Scatter plot and linear regression lines together with 95% prediction bands of $t_{\text{mean}}$ versus $t_{\text{surface}}$ (A), $t_{\text{core}}$ versus $t_{\text{surface}}$ (B) and $t_{\text{mean}}$ versus $t_{\text{core}}$ (C). Regression equations are understood with times in minutes, temperatures in °C and pouch width in cm.
Conclusion

The "30-minutes rule in transfusion medicine" is an appropriate estimate for RBC core temperature not exceeding 10°C. RBC mean and surface temperatures, however, exceed 10°C usually earlier.

References


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