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ORIGINAL RESEARCH

TRANSFUSION

The effect of the interruption of agitation, temporary cooling, and pneumatic tube transportation on platelet quality during storage for transfusion

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Abstract

Background: Conditions during blood product storage and transportation should maintain quality. The aim of this in vitro study was to investigate the effect of interruption of agitation, temporary cooling (TC), and pneumatic tube system transportation (PTST) on the aggregation ability (AA) and mitochondrial function (MF) of platelet concentrates (PC).

Study Design and Methods: A PC was divided equally into four subunits and then allocated to four test groups. The control group (I) was stored as recommended (continuous agitation, 22 ± 2°C) for 4 days. The test groups were stored without agitation (II), stored as recommended, albeit 4°C for 60 minutes on day (d)2 (III) and PTST (IV). Aggregometry was measured using Multiplate (RocheAG; ADPtest, ASPItest, TRAPtest, COLtest) and MF using Oxygraph-2k (Oroboros Instruments). The basal and maximum mitochondrial respiratory rate (MMRR) were determined. AA and MF were measured daily in I and II and AA in III and IV on d2 after TC/PTST. Statistical analysis was performed using tests for matched observations.

Results: Eleven PCs were used. TRAP-6 induced AA was significantly lower in II when compared to I on d4 ($P = 0.015$*). In III the ASPItest was significantly lower ($P = 0.032$*). IV showed no significant differences. The basal and MMRR were significantly reduced over 4 days in I and II (for both rates in both groups: $P = <0.0001$*). No significant differences occurred on d4 ($P = 0.495$).

Conclusion: Our results indicate that ex vivo AA and MF of PCs are unaffected, even in no-ideal storage and transport circumstances with respect to agitation, temperature, and force.

1 | INTRODUCTION

Transfusion of platelet concentrates (PCs) is used to prevent or treat bleeding in patients with either a low platelet count or poor platelet function. Clinical efficacy, rapid availability and safety of platelet transfusion is of paramount importance. Hence, after blood donation and platelet processing, storage and transport conditions take center stage to hold up product quality during shelf-life. Here, potential effects of temporary changes in storage temperature, discontinuation of agitation and force during transportation are very interesting to know. On this basis, clinicians can be advised what to do when storage recommendations may have been violated for short periods of time.

Platelet transfusions are routinely available since the 1970s.[1] After performing life-span studies of stored platelets, Murphy et al. then recommended the storage of PCs at 22 ± 2°C under continuous agitation.[2,3] Life-span of platelets was longer when stored at room temperature rather than refrigerated and agitation prevented platelet packing.[2,3] Agitation is intended to maintain platelet function by reducing their mutual activation and improving oxygen supply and CO_2 elimination at a stable pH.[4] The storage bags are gas permeable to allow aerobic metabolism and thus prevent a drop in pH.[5] As bacterial growth and the associated risk of transfusion-transmitted infection increases over time, the recommended storage time of PCs is limited.[6] Both, the American Food and Drug Administration and the British guidelines recommend the usage of stored PCs for up to 5 days after collection.[7,8] According to the current recommendation of the German Medical Association, PCs can be stored over a period of four-days (4x24h, calculated from 12 PM of the removal day) at +22 ± 2°C under continuous agitation.[9]

However, platelets undergo a series of morphological changes and functional modifications over time despite appropriate storage, resulting in a reduction of clinical transfusion efficacy with respect to platelet count and function, termed Platelet storage lesion (PLS). PLS is characterized by an altered morphology, an increase of procoagulant properties as well as a reduced release of alpha granules and cytosolic proteins.[5] Furthermore, platelet activation increases over storage time and already activated platelets may be less effective after transfusion.[10]

In addition, an association between storage time and mitochondrial dysfunction has been described in the literature over the past years.[11]

In clinical everyday life the agitation may be interrupted for different (in particular organizational) reasons. Some blood product institutions deliver blood products using a pneumatic tube system, thereby submitting the platelets to major forces. Furthermore, due to human error, it occasionally occurs that PCs may be stored in a blood product refrigerator at 4°C.

Especially in emergency bleeding situation, rapid availability of PCs may save lives. Transport via pneumatic tube systems could ensure low turnaround times. The question arises whether the acceleration and deceleration forces during the transport could influence platelet function.

With respect to the controversial debate about the impact of the storage method and duration on the function of PCs, the aim of this in vitro study was to systematically investigate the effect of continuous agitation on aggregation ability and mitochondrial function of platelets. Furthermore, the study aimed to quantify the effects of cooling of the PCs, transportation in the pneumatic tube system of the University Hospital Frankfurt and interruption of agitation.

2 | MATERIALS AND METHODS

This study was approved by the ethics committee of the University Hospital of Frankfurt (428/13).

2.1 | Platelet collection

Platelet concentrates were provided as routinely produced pool PCs by the German Red Cross Blood Transfusion Service of Baden-Wuerttemberg - Hessen, Frankfurt/Main, Germany. The platelet count per preparation was in the range of 2.0-4.5 × 10,[11] which corresponds to a platelet concentration of about 740-1800 × 10^3/µL. The PCs had the blood groups 0 (n = 3), B (n = 3) and A (n = 5). After routine PC preparation, each PC was equally divided into four subunits by separation into smaller storage containers (CompoFlex P4224, 4F Platelet storage system for pediatric platelets, maximum 4 × 600 mL, Fresenius Kabi AG, 61346 Bad Homburg, Germany). Each of the four subunits was then assigned to one of the four test groups. Tables 1 and 2 provide an overview on storage methods, measuring times, and measuring methods of the four test groups.

2.2 | Aggregometric analyses

Platelet aggregation was measured performing Multiple Platelet Aggregometry using the Multiplate device (Roche AG, Grenzach, Germany), as described in Tóth et al.[12] The probes were diluted in fetal calf serum (Gibco, United States). Ex-vivo aggregation of the platelets was induced following stimulation with 0,2 mmol/L adenosin diphosphate (ADPtest), 15 mmoL/L arachidonic acid (ASPItest), 1 mmol/L thrombin receptor activating peptide-6 (TRAPtest)

TABLE 1 Overview on the four test groups

Group	Storage temperature	Agitation	Pneumatic tube system
I	22 ± 2°C	Yes	No
II	22 ± 2°C	No	No
III	4°C (for 60 min), otherwise 22 ± 2°C	Yes	No
IV	22 ± 2°C	Yes	Yes

TABLE 2 Details on timing of interventions and measurements

	Time				
Group	Day 1		Day 2	Day 3	Day 4
I	Production and splitting into 4 subunits	Multiplate/ Oxygraph	Multiplate/Oxygraph	Multiplate/Oxygraph	Multiplate/Oxygraph
II			Multiplate/Oxygraph	Multiplate/Oxygraph	Multiplate/Oxygraph
III			Intervention: Cold storage, multiplate		
IV			Intervention: Pneumatic tube system, multiplate		

and 100 µg/mL collagen (COLtest). The aggregation was quantified as area under the curve (AUC) to express the aggregation response over the measured time. AUC was recorded as Units (U).

2.3 | Determination of the mitochondrial respiratory rate

High-resolution respirometric measurements (mitochondrial oxygen consumption measurements) were performed with the Oxygraph-2k (Oroboros Instruments, Innsbruck, Austria). Oxygen in the Oxygraph chamber was measured with the OROBO-POS (polarographic oxygen sensor). The oxygen sensor can determine changes in the O_2 concentration at a high temporal resolution.[13]

Platelets were added to a chamber of the Oxygraph and diluted with SSP (Macopharma, 59420 Mouvaux, France). Respirometry was carried out with continuous mixing by means of an electromagnetic stir bar at 30°C. After 10 to 15 minutes, a plateau appeared in the O_2 flux curve (Basal rate). First, 1 µL oligomycin (2 mg/mL) was added. The inhibition of the adenosine triphosphate (ATP) synthase leads to the formation of a new plateau with significantly lower O_2 flux values (Oligomycin rate). Second, the respiratory chain decoupler carbonyl cyanide p-trifluoromethoxyphenylhydrazone (FCCP) was titrated in 1 µM increments. FCCP was titrated until the measured O_2 flow cannot be increased by further additions/drops (Maximum mitochondrial respiratory rate). At last, 0.016 µmol of potassium cyanide (KCN, respiratory chain inhibitor) were added which causes an abrupt drop in the O_2 consumption (KCN rate). The measured oxygen consumption was expressed in pmol/(s*mL). The higher the oxygen consumption the more active is the respiratory chain.

2.4 | Measurement sequence

Measurements with the Multiplate and Oxygraph were performed daily in group I. The measurements on day 1 in group I were carried out approximately 2 hours after subunit division. On day 1 the measurements took only place in group I, because after PC preparation each PC was equally divided into four subunits. We therefore assumed that shortly after the division all four subunits have the same properties. This means that the measurement from group I on day 1 is used as a reference and baseline of aggregation and metabolic activity on day 1 and therefore representative for all four groups on day 1. The consecutive measurements with the Multiplate and the Oxygraph in group I and II took place after further 24 hours (day 2), 48 hours (day 3), and 72 hours (day 4) of storage.

The interventions temporary cooling (group III) and transportation in the pneumatic tube system (group IV) were carried out after approximately 24 hours of storage under continuous agitation at 22 ± 2°C. Group III was stored under 4°C for 60 minutes on day 2. The average temperature reduction was 17°. Measurements were performed approximately 40 minutes later at room temperature. Group IV was transported in the pneumatic tube system of the

University Hospital Frankfurt (Swisslog Rohrpostsysteme GmbH) twice on day 2. The transportation speed in the system was 2-3 m per second. The throughput time varied between 12 minutes, 35 seconds and 14 minutes, 15 seconds.

2.5 | Statistics

Statistical analyses were performed using Prism (Version 5, GraphPad Software, Incorporated, La Jolla, California, United States) and BiAS for Windows (Version 11.02-03/2016, epsilon-publisher, Dr. Ackermann, Goethe-University Frankfurt).

Depending on the distribution of the data from Shapiro-Wilk-test, the results are given as the mean (SD) or the median (25th and 75th percentiles, interquartile range). Potential differences between two groups were analyzed using the paired *t* test or the Wilcoxon matched pairs test. To compare results from three or more days with matched observations repeated measures tests were used. If the data was distributed normally the *repeated measures* analysis of variance (*ANOVA)* test was used. Significant results were further analyzed with *multiple comparison Scheffé test*. If the data was not normally distributed, the Friedman´s test together with Multiple Conover-Iman comparisons with Bonferroni-Holm-Correction was applied.

3 | RESULTS

This study included 11 PCs in which aggregation ability and mitochondrial respiratory rate were examined over the course of 4 days.

3.1 | Aggregation ability

3.1.1 | Effect of agitation vs non-agitation on aggregation parameters

In the statistical analysis of the aggregation tests the results from day 1 to day 4 of the control group (group I - under agitation) were analyzed first. The results from group I at day 1 are the baseline aggregation measurements. Then the results of the test group II from day 2 to day 4 (group II - omitted agitation) and the results from group I, day 1 were compared.

As shown in Figures 1, 2, and 3, in the control group (group I) the ADPtest ($P = 0.991$), TRAPtest ($P = 0.151$) and COLtest ($P = 0.071$) did not differ significantly within the 4 days. When stimulated with arachidonic acid (ASPItest), the AUC was significantly higher on day 4 (Figure 4). The ASPItest showed a significant result over time when comparing all 4 days ($P = 0.018$*) with the *Friedman´s test*.

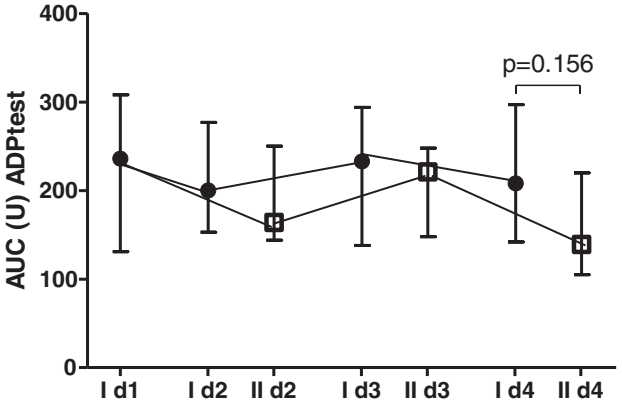

FIGURE 1 Platelet aggregation following stimulation with adenosine diphosphate (ADPtest) in subunits of PCs under agitation (group I ●) and with omitted agitation (group II □). (median, interquartile range). The results from group I at day 1 are the baseline aggregation measurements. ADP, adenosin diphosphate; AUC, area under the curve; d, day; U, Units

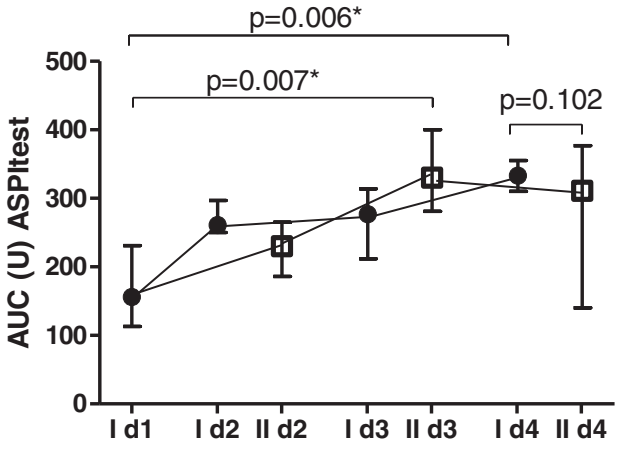

FIGURE 2 Platelet aggregation following stimulation with thrombin receptor activating peptide-6 (TRAPtest) in subunits of PCs under agitation (group I ●) and with omitted agitation (group II □). (median, interquartile range). The results from group I at day 1 are the baseline aggregation measurements. AUC, area under the curve; d, day; TRAP-6, thrombin receptor activating peptide-6; U, Units

The ASPItest was also significantly different over time in the test group (group II; $P = 0.0047$*) when comparing all 4 days. The ADPtest ($P = 0.475$), TRAPtest ($P = 0.220$) and COLtest ($P = 0.058$) did not differ significantly within the 4 days in the test group.

Afterward, a paired test was performed between group I day 4 and group II day 4. In the ADPtest, ASPItest and COLtest the control group showed no significantly different values compared to the test

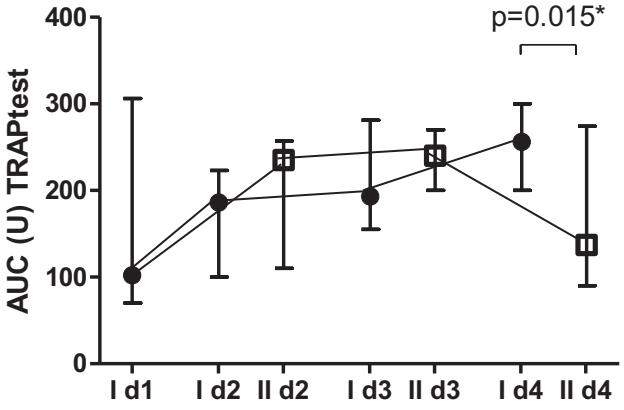

FIGURE 3 Platelet aggregation following stimulation with collagen (COLtest) in subunits of PCs under agitation (group I ●) and with omitted agitation (group II □). (median, interquartile range). The results from group I at day 1 are the baseline aggregation measurements. AUC, area under the curve; COL, collagen; d, day; U, Units

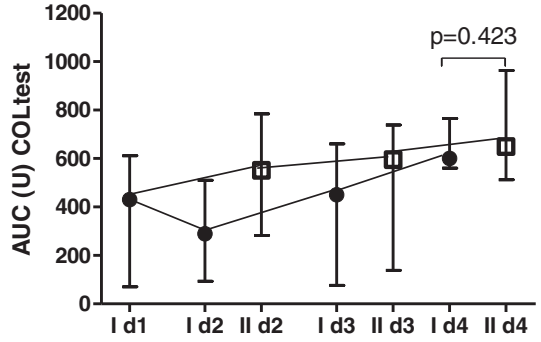

FIGURE 4 Platelet aggregation following stimulation with arachidonic acid (ASPItest) in subunits of PCs under agitation (group I ●) and with omitted agitation (group II □). (median, interquartile range). The results from group I at day 1 are the baseline aggregation measurements. ASPI, arachidonic acid; AUC, area under the curve; d, day; U, Units

group on day 4. In the TRAPtest, however, the values were significantly lower in the test group [mean ± SD: group I day 4, 250.5 ± 65.2 U; group II day 4, 159.6 ± 98.4 U; $P = 0.015$*].

3.1.2 | Effect of cooling on aggregation parameters

The effect of cooling was also measured with all four aggregation tests. In the ADPtest, ASPItest, and TRAPtest the mean results were lower in group III which was cooled compared to the control group (group I) on day 2 [mean ± SD: ADPtest group I 217.5 ± 77.24 U vs group III 179.5 ± 87.66 U, $P = 0.315$; ASPItest group I 251.4 ± 56.93 U vs group III 187.4 ± 78.58 U, $P = 0.032$*; TRAPtest group I 177.3 ± 66.29 U vs group III 175.4 ± 99.43 U, $P = 0.955$]. But only in the ASPItest the results were significantly lower in the cooling test group ($P = 0.032$*). Measurements in the test group with the COLtest were higher compared to the control group [mean ± SD: COLtest group I 307.4 ± 240.1 U vs group III 398.9 ± 279.0 U, $P = 0.368$].

3.1.3 | Effect of transport through the pneumatic tube system on aggregation parameters

The analysis after transportation in the pneumatic tube system showed no significant difference [mean ± SD: ADPtest group I 217.5 ± 77.24 U vs group IV 214.4 ± 73.74 U, $P = 0.881$; ASPItest group I 251.4 ± 56.93 U vs group IV 192.47 ± 103.7 U, $P = 0.1055$; TRAPtest group I 177.3 ± 66.29 U vs group IV 185.4 ± 108.5 U, $P = 0.7371$; COLtest group I 307.4 ± 240.1 U vs group IV 456.5 ± 214.8 U, $P = 0.0604$]. Here, only 10 instead of 11 subunits were compared because one subunit did not return from its run in the pneumatic tube system on day 2 and only reappeared the next morning.

3.1.4 | Mitochondrial respiratory rate

First, we analyzed with multiple comparison tests, both in the control group (group I) and in the test group (group II), whether the respiratory rate changes significantly over the duration of 4 days of storage. In the control group (group I) the Basal rate ($P = <.0001$*), Oligomycin rate ($P = 0.0286$*), Maximum rate ($P = <.0001$*), and KCN rate ($P = 0.0015$*) were significantly different over time. Similar results are also shown by the measurements within the test group (group II). Also, in the test group the Basal rate ($P = <.0001$*), Oligomycin rate ($P = 0.0010$*), Maximum rate ($P = <.0001$*), and KCN rate ($P = 0.0057$*) were significantly different over time.

The descriptive statistics and the test results show that the basal mitochondrial respiratory rate and the maximum mitochondrial respiratory rate are reduced significantly over time in the control and in the test group. Figure 5 illustrates the basal mitochondrial respiratory rate of group 1 and 2 over time and Figure 6 illustrates the maximum mitochondrial respiratory rate of group 1 and 2 over time.

Furthermore, we analyzed whether the respiratory rates are different between group I and group II on day 4. The respiratory rates on day 4 were not significantly different

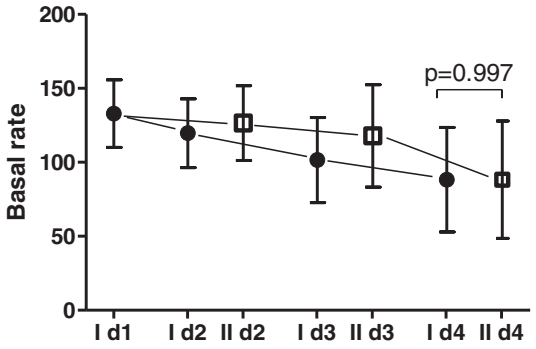

FIGURE 5 Basal mitochondrial respiratory rate in pmol/(s*mL) in subunits of PCs under agitation (group I ●) and with omitted agitation (group II □). (mean ± SD). The results from group I at day 1 are the baseline aggregation measurements. d, day

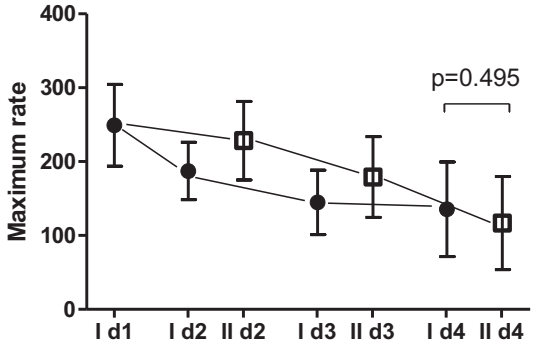

FIGURE 6 Maximum mitochondrial respiratory rate in pmol/(s*mL) in subunits of PCs under agitation (group I ●) and with omitted agitation (group II □). (mean ± SD). The results from group I at day 1 are the baseline aggregation measurements. d, day; MMRR, maximum mitochondrial respiratory rate

between group I and group II (Basal rate $P = 0.997$, Oligomycin rate $P = 0.865$ and Maximum rate $P = 0.495$).

4 | DISCUSSION

PCs are transfused to prevent or treat coagulopathy and bleeding. Product quality and clinical efficacy is therefore highly important for patient safety. In clinical everyday life storage conditions may deviate from recommendations with respect to temperature and movement during storage and transport, which may lead to platelet activation and/or dysfunction. Our study aimed to assess the influence of modes of transport and deviation from recommended storage conditions on the functional parameters of platelets stored for transfusion. We assessed aggregation ability and mitochondrial function.

The results of our study suggest that mitochondrial function decreases significantly during the up to 4 days of storage under agitation at 22 ± 2°C.

Perales Villarroel et al. also examined mitochondrial function in stored PCs.[11] In line with our results, their measurements with the Oxygraph showed a significant decrease over storage time in all measured respiratory capacities.

In clinical reality, agitation may sometimes be interrupted due to organizational problems or human error. We therefore wanted to know whether this would result in loss of function or a decrease in product quality. Therefore, we analyzed whether the omission of agitation would impact the respiratory rates. We found that the basal mitochondrial respiratory rate and the maximum mitochondrial respiratory rate were also significantly reduced over 4 days in the group with omitted agitation. No significant differences were found between the control group (continuous agitation) and test group (omitted agitation) on day 4.

In general, mitochondria play an important role in homeostasis of platelets or cells.[14,15] The source of ATP of cells are anaerobic glycolysis and oxidative phosphorylation.[16] Therefore, intracellular ATP levels decline with reduced function of the respiratory chain, which seems to be the case in stored PCs. The respiratory rate of thrombocytes decreases over time, regardless of continued agitation or omitted agitation. The question arises as to which effect the diminished function of the respiratory chain in vitro could have on the function of the platelets after transfusion in vivo. Under the assumption that the mitochondrial rate is a surrogate parameter for product quality, this could possibly imply that PCs could be transfused to patients, even if they have been stored incorrectly for a short time. However, we do not know whether the thrombocytes function well in vivo as this has not been demonstrated in our study.

To draw conclusions on the actual function of the thrombocytes, we then analyzed the aggregation ability in vitro with the Multiplate Analyzer.

In the control group only ASPI induced platelet aggregation showed a significantly higher AUC on day 4 compared to day 1. Aggregation was therefore not negatively influenced by recommended storage conditions.

In the ASPI test, the aggregation ability seems to improve in tests over the course of the days. A possible explanation would be a temporary decrease of the activation ability due to the manufacturing process for example, foreign surfaces and centrifugation. Potentially, the function improves because they recover from it over the course of the days. This effect is known from other studies in which platelets suffer from stressors such as the heart-lung machine. A study by Rinder et al. for instance showed that cardiopulmonary bypass operations with membrane oxygenator produce selective decreases in surface glycoproteins Ib and IIb/IIIa as well as in platelet

activation.[17] These alterations were temporary and could be due to shear stress due to the membrane oxygenator. A study by Varghese et al. also showed these effects.[18] Similarly, for example, shear forces could affect the platelets during the PC manufacturing process.

The study by Perales Villarroel et al. also investigated aggregation ability.[11] In contrast to our results, the activation decreased significantly over time.

We also analyzed whether it makes a difference on day 4 if the PCs were stored under agitation or with omitted agitation. Only TRAP induced platelet aggregation showed a significantly lower aggregation ability in the test group. These results imply discontinuation of agitation reduce aggregation ability. Nonetheless, PCs tolerated a day or two without agitation until significant changes in aggregation ability were measured.

In this study, the possible influencing factors of cold storage and extreme shaking in the pneumatic tube system of the hospital were also investigated. ASPI induced platelet aggregation was negatively influenced by cooling. None of the aggregation measurements showed significant influence of transport with the pneumatic tube system.

Storage temperature is also a matter of debate in other studies as cold storage may have bacteriostatic effects and would therefore allow for a longer storage period and possibly higher transfusion safety. In a study by Reddoch et al.,[19] paired samples from five PCs were stored at room temperature with agitation, at 4°C with agitation and at 4°C without agitation. Stimulation with ADP and collagen showed significantly better aggregation responses on day 3 and 5 in cold-stored platelets (agitation and omitted agitation) compared to platelets stored at room temperature. However, TRAP induced aggregation showed decreased responses in all groups with no significant differences between the groups.

Two other studies examined platelets after transportation in a pneumatic tube system. Sandgren et al.[20] found no statistically significant differences in lactate production and pH between the control group and PCs which ran through the pneumatic tube system. Lancé et al. examined aggregation parameters.[21] Collagen- and ADP induced aggregation measurements showed no influence of transport. Only TRAP induced platelet aggregation was negatively influenced by multiple transport.

Two studies have investigated the function of platelets after transfusion in vivo. In the study by Roeloffzen et al. transfused platelets regained function in vivo, but hemostatic potential of PCs stored for 1-3 days compared to PCs storage for 4-5 days was higher.[22] Also, in a study by Vetlesen et al. the recovery and survival rate of platelets in vivo was higher when PCs stored for 1-3 days than PCs stored for 3-6 days were transfused, whereas activation potential was about equal.[23] Differences in results could be due to the fact that Roeloffzen et al. used pooled PCs and analyzed hemostatic potential based on clotting time and the rate of clot growth[22] whereas Vetlesen et al. used apheresis PCs and activation potential was assessed by measuring the expression of the surface activation markers CD63 and CD62P or by CD42a.[23]

One limitation of our study is that all measurements were carried out in vitro. A possible improvement to the study would be to include additional measurements with the Oxygraph after cooling or transport in the pneumatic tube system. Possible extension of the study would have been in vivo measurements or the additional use of other methods such as the measurement of surface markers on platelets or the measurement of traditional markers of platelet viability and metabolism (eg, platelet count, pH). A strength of our study is that each PC served as its own control as each PC was divided into four equal parts.

In conclusion, this study demonstrates that the mitochondrial respiratory rate in PCs is not significantly different when comparing PCs under agitation and omitted agitation over 4 days. This implies that no difference in mitochondrial function appear, even if the PCs were not agitated, contrary to the recommendation. In PCs under agitation and omitted agitation the respiratory rate decreased over time, whereas aggregation ability was mostly not significantly influenced by storage time.

Due to the facts that the mitochondrial respiratory rate decreases in a similar amount when PCs are stored without agitation and PCs tolerated a day or two without agitation until significant changes in aggregation ability were measured, we would conclude that a product is still of good quality for transfusion after short times of (incidental) cessation instead of continuous agitation.

Furthermore, our results show that it is feasible to deliver PCs in the pneumatic tube system, especially if this reduces the time-to-treat in acute bleeding situations.

Future prospective in vivo studies should clarify if these observations are associated with clinical outcomes, including bleeding, thrombosis or mortality in critically ill or hematology patients.

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Institution: Goethe-Universitat Frankfurt am Main Blended DEAL: ProjektDEAL.

CONFLICT OF INTEREST

SB, SK, EHA, and DF declare that they have no conflicts of interest relevant to the manuscript submitted to TRANSFUSION. MMM is an employee of the German Red Cross Blood Transfusion Service Baden-Wuerttemberg-Hessen and received an honorarium as well as support in travel and hotel costs for a lecture from TerumoBCT. CFW received travel support and honoraria for scientific lectures from Roche AG, Werfen, Dynabyte and enicor. KZ received grants from CSL Behring, Serumwerke, Vifor Pharma, Johnson & Johnson, Schöchl Medical, Fresenius Kabi, Fresenius Medical, AIT Wien, B. Braun Melsungen, Biotest AG, Edwards Livescience, Forum Sanitas, Haemonetics Corporation, Hexal AG, Masimo International, Nordic Pharma, Nordic group, Ratiopharm, TEM International, Siemens.

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