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BLOOD COMPONENTS

TRANSFUSION

Platelet function of whole blood after short-term cold storage: A prospective in vitro observational study

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Abstract

Background: There is no standardized storage temperature of whole blood for acute normovolemic hemodilution (ANH).

Study Design and Methods: We conducted a prospective observational study to examine the difference in platelet function between short-term whole blood storage at 4 and 22°C. Venous blood (40 ml) was collected from seven healthy subjects who gave prior written consent. The samples were divided into three groups: before storage (group Pre), cold (4°C) storage (group C), and room temperature (22°C) storage (group R). Groups C and R were tested after 6 h of blood storage. Platelet aggregability, platelet factor 4 (PF4), β-thromboglobulin (β-TG), P-selectin expression, pH, PO_2, PCO_2, glucose, lactate, blood count, and thromboelastography (TEG) parameters were measured. The percentage change in each parameter in groups C and R was calculated using the value in group Pre as a reference. These data were then compared between groups C and R using a Wilcoxon matched pairs test. $p < 0.05$ was considered to be statistically significant.

Results: Compared with group R, group C showed significantly higher platelet aggregability with adenosine diphosphate (ADP) 2, 4, and 6 μM (all $p = 0.016$) and collagen 1 μg/ml ($p = 0.047$) stimulation, and significantly lower PF4 and β-TG elevation (both $p = 0.031$), glucose consumption ($p = 0.031$), and lactate production ($p = 0.016$). The ADP channel in TEG showed a significant increase in platelet aggregation rate in group C compared to group R.

Discussion: Cold storage of whole blood in ANH may provide improved storage conditions for platelets and contribute to improved hemostasis compared to room temperature storage.

KEYWORDS

acute normovolemic hemodilution, cold temperature, platelet aggregation, platelet factor 4, P-selectin

Abbreviations: ADP, adenosine diphosphate; ANH, acute normovolemic hemodilution; ATP, adenosine triphosphate; β-TG, β-thromboglobulin; CPDA, citric-phosphate-dextrose-adenine; MCV, mean corpuscular volume; MPV, mean platelet volume; PBS, phosphate-buffered saline; PF4, platelet factor 4; PPP, platelet-poor plasma; PRP, platelet-rich plasma; PSLs, platelet storage lesions; RBC, red blood cell; ROTEM, rotational thromboelastometry; SDs, standard deviations; TCA, tricarboxylic acid cycle; TEG, thromboelastography.

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1 | INTRODUCTION

Although recent improvements in surgical techniques have reduced the amount of intraoperative blood loss in many procedures,[1–3] there are still many situations in which massive blood loss occurs, forcing the use of large amounts of transfusion products. However, the supply of allogenic blood transfusion products may become insufficient in the future due to the ongoing global aging population.[4–6] Thus, acute normovolemic hemodilution (ANH), a method of autologous blood transfusion, deserves attention. In ANH, blood is donated immediately before an operation and transfused at the end of surgery. This method is recommended by the American Society of Anesthesiologists to reduce allogenic blood transfusion in patients at high risk for excessive bleeding.[7] Nonetheless, there is still no standardized storage method of blood for ANH[8] because of the limited evidence.

In the 1960s and 1970s, platelet products were kept in cold storage as a standard of care.[9] However, this procedure was abandoned due to the extremely short life of platelets in cold storage,[10] and it is now common to store platelet products at room temperature of 20–24°C.[11] Recently, however, the utility of cold-stored platelets has been suggested, particularly in trauma resuscitation and surgical bleeding.[12] In response, the U.S. Food and Drug Administration approved the use of cold-stored apheresis platelets for resuscitation in cases of bleeding.[13]

These studies raise concerns with regard to room temperature storage of whole blood for ANH in terms of platelet function. Therefore, we conducted a prospective in vitro study to investigate the effects on platelet function of the storage temperature (4°C or 22°C) of whole blood for 6 h.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

This prospective observational cohort study was conducted from 10 February 2021 to 21 April 2022 in the Department of Anesthesia, Kyoto University Hospital, with the approval of the Ethics Committee of Kyoto University Hospital (No. R0978-1). The study was carried out according to the guidelines of the Declaration of Helsinki. Prior written informed consent was obtained from all subjects.

2.2 | Participants and groups for blood storage

Subjects who met the following three criteria were included in the study: (1) healthy adults aged 20–65 years who (2) were not taking blood coagulation-related medication and (3) had no blood coagulation-related diseases. According to the aim of the study, whole blood was examined (1) before storage (group Pre), (2) after storage at a cold temperature (4°C) for 6 h (group C) and (3) after storage at room temperature (22°C) for 6 h (group R).

2.3 | Blood preparation and materials

The temperature in the laboratory was strictly controlled to 22°C ± 1°C. Venous blood (30 ml) was drawn from each subject using a syringe preloaded with a 10% volume of citric-phosphate-dextrose-adenine (CPDA) fluid, removed from a blood bag containing blood storage solution (Karmi CA, SB-Kawasumi Laboratories, Inc., Kanagawa, Japan), and another 10.1 ml was collected without CPDA. The composition of CPDA was citric acid hydrate 0.327 w/v%, sodium citrate hydrate 2.630 w/v%, monobasic sodium phosphate 0.251 w/v%, dextrose 2.900 w/v%, and adenine 0.0275 w/v%. The 30 ml of blood collected with CPDA were equally divided into three syringes for use in each group. Of the 10.1 ml of blood without CPDA, 2 ml was dispensed into a heparin-containing tube and equally divided into three microtubes, again for use in each group. The remaining 8.1 ml was equally divided into three citrate-containing tubes for the three groups. The blood samples in groups C and R were stored at 4°C or 22°C for 6 h with air removed.

Adenosine diphosphate (ADP) (Nacalai Tesque, Kyoto, Japan), a platelet stimulating agent, was diluted to 200 μM in phosphate-buffered saline (PBS). Collagen (Sakae Corp., Tokyo, Japan), another platelet stimulating agent, was diluted to 100 μg/ml in the provided diluent storage solution. The following antibodies (Becton Dickinson Japan, Tokyo, Japan) were used for flow cytometry: peridinin chlorophyll protein-labeled anti-CD61 antibody, which recognizes the CD61 antigen present on all human platelets; and phycoerythrin-labeled anti-CD62P (P-selectin) antibody, which recognizes the CD62P antigen expressed on activated platelets and is a marker of platelet storage lesions (PSLs). A 10-fold dilution of 1% formaldehyde and 0.1% sodium azide (CellFIX™ 10X, BD Biosciences, Franklin Lakes, NJ, USA) was used for specimen fixation.

A platelet aggregation assay was performed with a light transmission aggregometer (MCM Hema Tracer 212, MC Medical, Tokyo, Japan). Citrate-containing blood collection tubes and polyethylene tubes (SRL, Inc., Tokyo, Japan) were used to measure platelet factor 4 (PF4) and β-thromboglobulin (β-TG), both of which are platelet-derived cytokines and markers of PSLs. An automated cell analyzer (FACSCalibur™, Becton Dickinson, San Jose, CA, USA) and a computer software to acquire and

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analyze data from the cell analyzer (CellQuest™ Pro Version 5.2, Becton Dickinson, San Jose, CA, USA) were used for flow cytometry. A blood gas analyzer (RAPIDPoint® 500, Siemens Healthineers, Munich, Germany) was used for blood gas analysis. An automated blood cell analyzer (Celltac α, Nihon Kohden Corp., Tokyo, Japan) was used for blood counts and measurement of the platelet-rich plasma (PRP) concentration. Thromboelastography (TEG) parameters indicative of blood viscoelasticity were measured using heparin-containing blood collection tubes, a blood coagulation analyzer (TEG®6 s, Haemonetics Japan GK, Tokyo, Japan) and cartridges that can assess platelet function (PlateletMapping® ADP, Haemonetics Japan GK, Tokyo, Japan).

2.4 | PRP preparation

Platelet aggregability and P-selectin expression were measured using PRP with platelet counts adjusted to 250×10^9/L by dilution with platelet-poor plasma (PPP). PRP was collected as the supernatant obtained by centrifuging whole blood at 160 g for 10 min at 22°C; and PPP as the supernatant from centrifuging the residue after removal of the PRP for another 1,600 g for 15 min at 22°C.

2.5 | Procedures for each test

2.5.1 | Platelet aggregability

Light transmission rates of PRP were measured for 7 min after a platelet-stimulating agent (ADP 2, 4, 6 μM; collagen 1, 2, 3 μg/ml) was added. The control was PPP (100% light transmittance). Two consecutive measurements were taken and the average of the maximum values was used as the result.

2.5.2 | PF4 and β-TG

Citrate tubes were centrifuged at 2,000 g for 30 min at 4°C. Each supernatant was dispensed into a polyethylene tube and submitted to SRL, Inc. for PF4 and β-TG assays. When PF4 and β-TG were out of the measurement range, the results were set at the upper limits of 100 and 200 ng/ml, respectively.

2.5.3 | P-selectin expression

PRP was diluted 10-fold with PBS and left to stand for 15 min at 22°C, followed by fixation with CellFIX at 4°C. Centrifugation at 1600 g for 15 min at 4°C and washing with PBS were then repeated twice, followed by the addition of 1 μl each of anti-CD61 antibody and anti-P-selectin antibody. Flow cytometry was performed as previously reported[14] after the samples were left standing in the dark for 1 h at 22°C. The mean fluorescence intensity of CD62P-positive platelets among 10,000 CD61-positive platelets was calculated.

2.5.4 | Blood gas

Since PSLs are attributed to platelet metabolism,[15] blood gas analysis was performed to determine if different storage temperatures affected platelet metabolism and hence PSLs. The following five parameters were measured: pH, PO_2, PCO_2, glucose, and lactate.

2.5.5 | Blood count

Platelet count and mean platelet volume (MPV) were measured to assess platelet function, and red blood cell (RBC) count and mean corpuscular volume (MCV) were measured to assess RBC function.

2.5.6 | TEG

TEG measures the speed and strength of coagulation, and provides a rapid global assessment of hemostatic function, including the parameters R (time until clot formation starts), K (rate of clot formation), and MA (maximum clot strength).[16] The TEG 6s PlateletMapping cartridge has four channels: kaolin/heparinase (HKH), reptilase/factor XIIIa/abciximab (ActF), ADP/ActF (ADP) and arachidonic acid/ActF (AA).[17] Seven parameters were measured: R-HKH, K-HKH, and MA-HKH, which are the R, K, and MA values measured using HKH; MA-ActF, the MA value measured using ActF; MA-HKH minus MA-ActF, the difference between MA values measured using HKH and ActF; and Aggregation-ADP and MA-ADP, the aggregation rate and MA measured using ADP.

2.6 | Statistical analysis

For each test in each subject, the percentage changes of values in groups C and R were calculated using the values in group Pre as a reference: value in group C or R/value in group Pre × 100 (%). Results are presented as means, standard deviations (SDs), standard errors, and 95% confidence intervals. The % changes in groups C and R were compared using a Wilcoxon matched pairs test with Prism 9 for macOS ver. 9.3.1 (GraphPad). A two-

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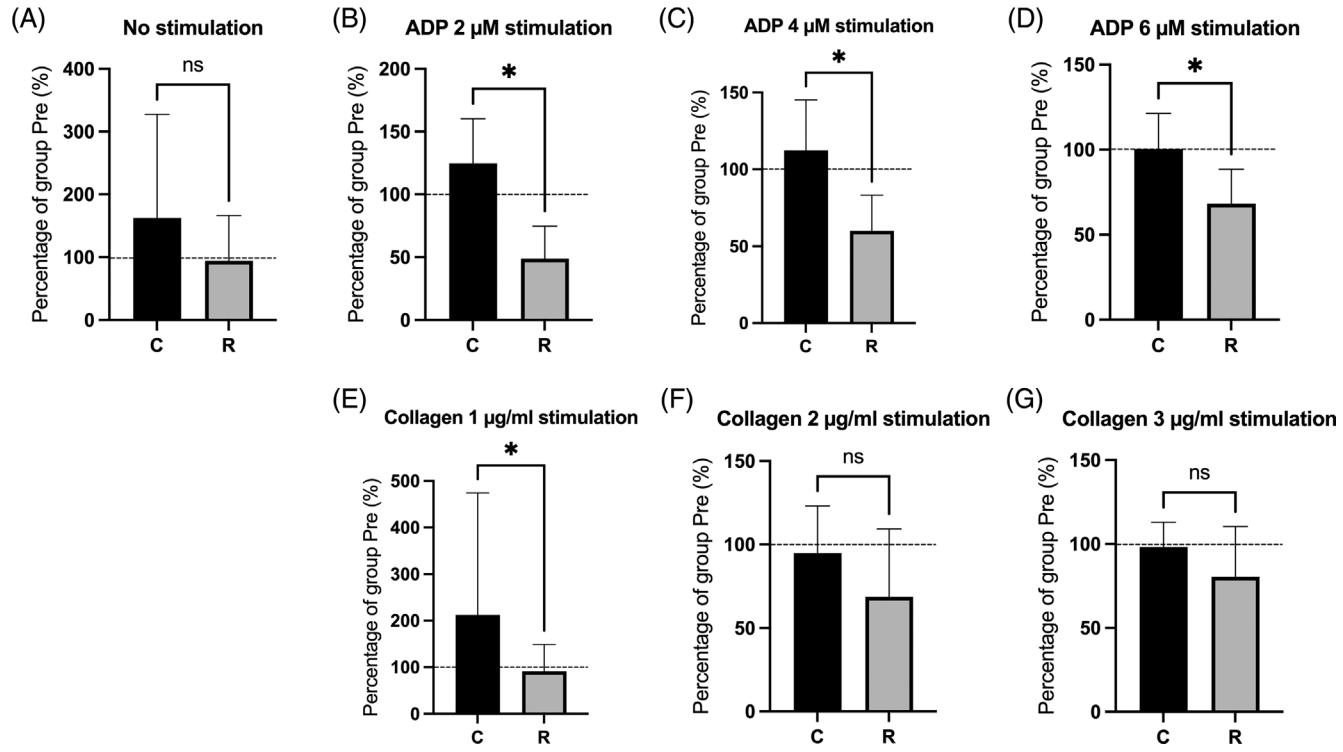

FIGURE 1 Maximum platelet aggregation rates shown as % changes in groups C and R relative to group pre. Means ± SD are shown on the graphs. (A) Aggregation rates without platelet stimulants ($n = 6$). (B–G) Aggregation rates with platelet stimulants (ADP or collagen) ($n = 7$). Values for ADP 2, 4, and 6 μM and collagen 1 μg/ml stimulation showed significant differences between groups C and R.

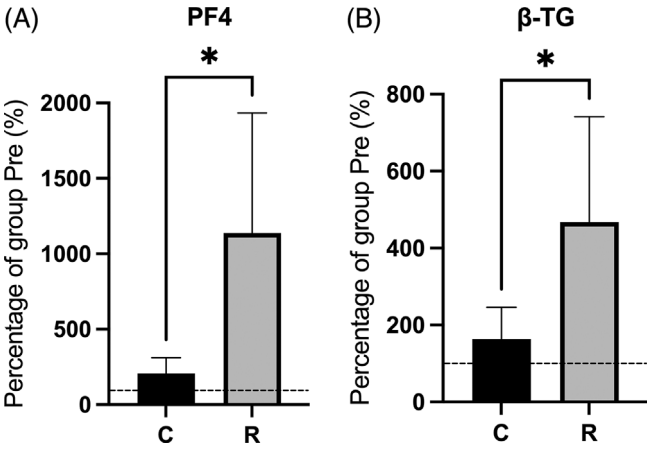

FIGURE 2 PF4 and β-TG levels shown as % changes in groups C and R relative to group pre ($n = 6$). Means ± SD are shown on the graphs. Both parameters showed significant differences between the two groups.

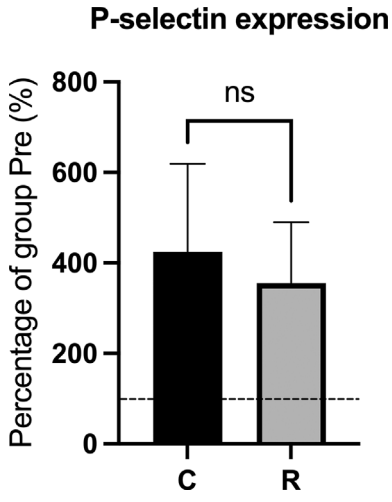

FIGURE 3 Mean fluorescence intensities of P-selectin shown as % changes in groups C and R relative to group pre ($n = 7$). Means ± SD are shown on the graphs. There was no significant difference between the two groups.

sided α <0.05 was considered to be statistically significant. Based on a difference of 1.5 times the standard deviation being clinically significant, a power of 0.80, and an α level of 0.05, about 6 subjects were needed to show significance. With an estimated dropout rate of 15%, we included 7 subjects in the study. All data and statistics are shown in Tables S1 and S2.

3 | RESULTS

Blood samples were collected from 7 subjects. Due to missing data for several parameters in one subject, data for 6 or 7 subjects are shown for each parameter. The

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means and SDs for the % changes in groups C and R relative to group Pre are shown in Figures 1–6.

3.1 | Platelet aggregability

The platelet aggregation rates (Figure 1) under ADP 2 μM ($p = 0.0156$, Figure 1B), 4 μM ($p = 0.0156$, Figure 1C), 6 μM ($p = 0.0156$, Figure 1D), and collagen 1 μg/ml ($p = 0.0469$, Figure 1E) stimulation were significantly higher in group C than in group R.

3.2 | PF4 and β-TG

PF4 and β-TG (Figure 2) were markedly elevated in group R and were significantly higher than those in group C (both $p = 0.0312$).

3.3 | P-selectin expression

P-selectin expression (Figure 3) did not differ significantly between groups C and R ($p = 0.2188$).

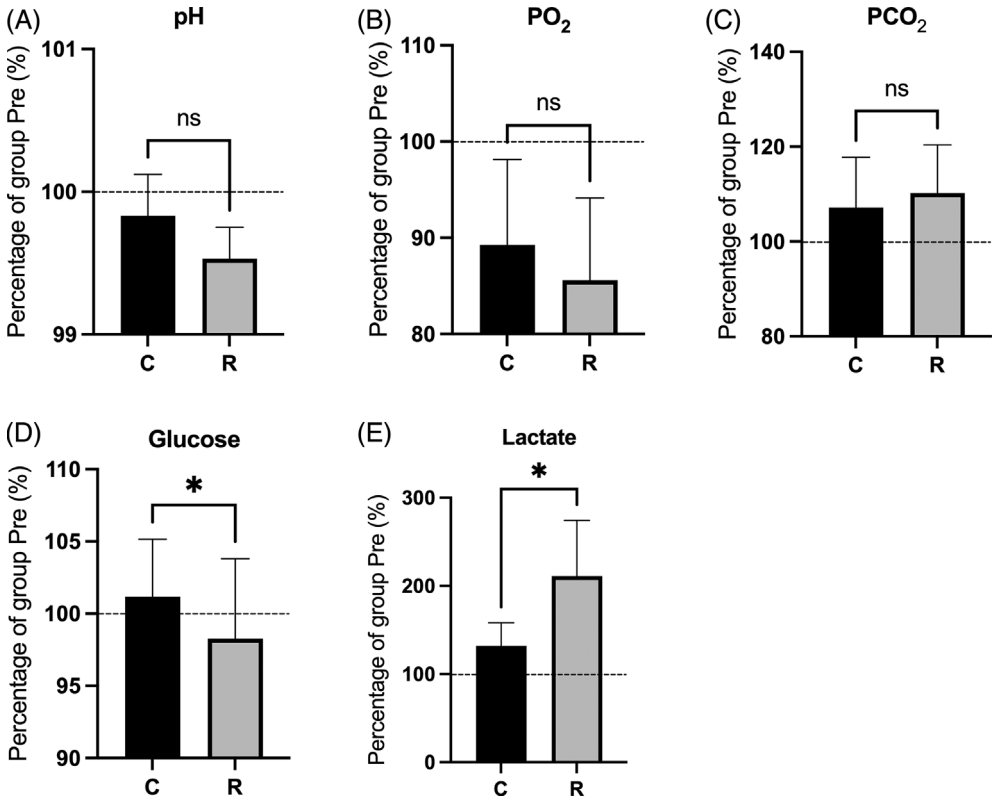

FIGURE 4 Blood gas parameters shown as % changes in groups C and R relative to group pre ($n = 7$). Means ± SD are shown on the graphs. There were significant differences between the two groups for glucose and lactate.

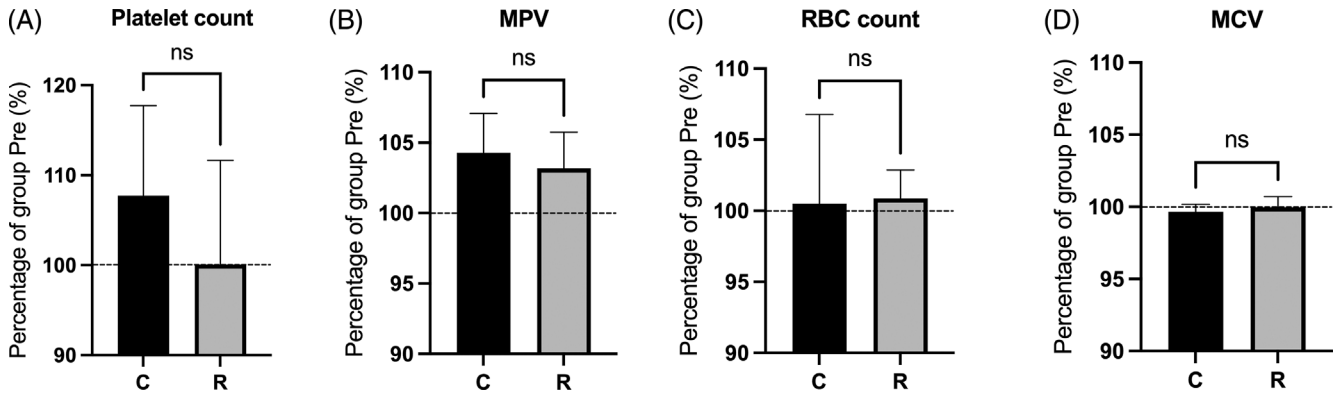

FIGURE 5 Blood counts shown as % changes in groups C and R relative to group pre ($n = 7$). Means ± SD are shown on the graphs. There was no significant difference in platelet count, MPV, RBC count, or MCV between the two groups.

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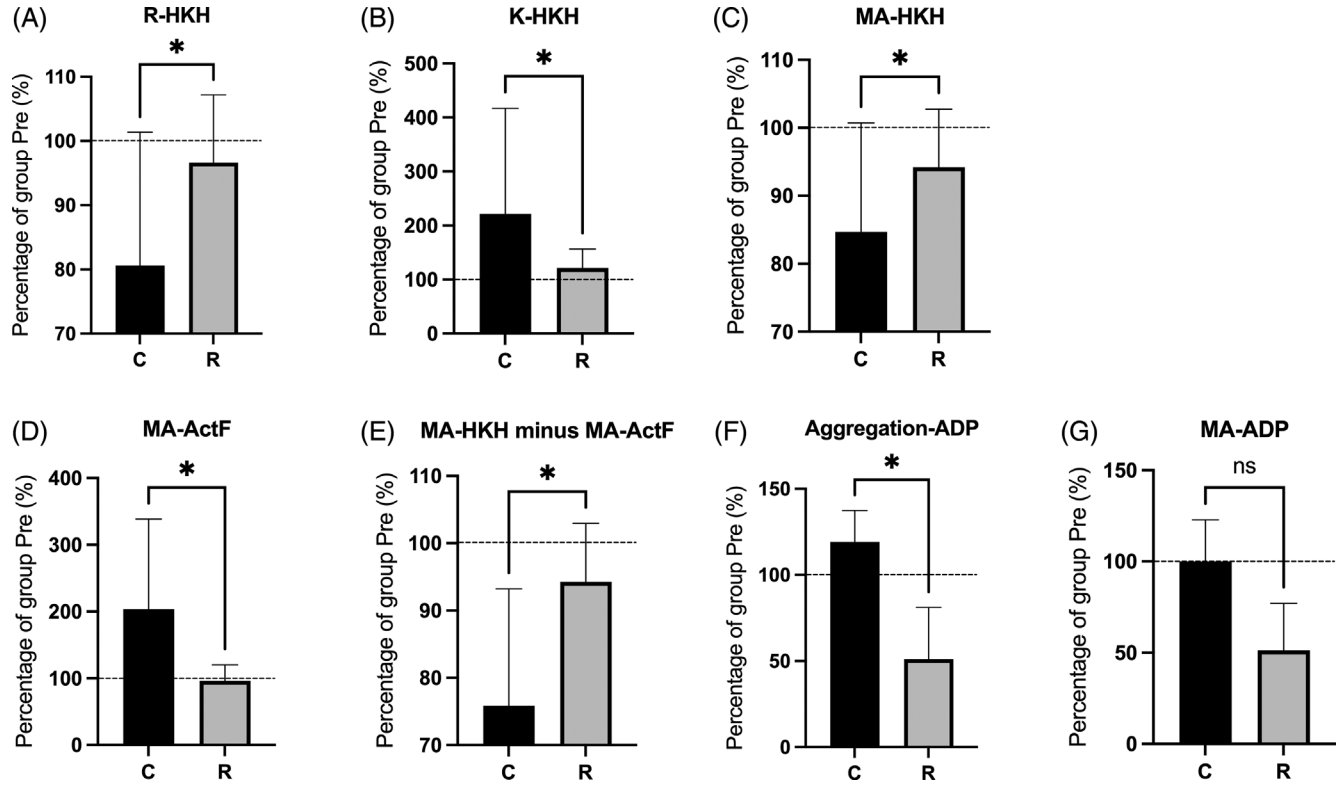

FIGURE 6 TEG 6s PlateletMapping parameters shown as % changes in groups C and R relative to group pre ($n = 7$). Means ± SD are shown on the graphs. There were significant differences in all parameters except for MA-ADP between the two groups.

3.4 | Blood gas

Blood gas values (Figure 4) in groups C and R showed no significant difference for pH ($p = 0.0625$, Figure 4A), PO_2 ($p = 0.1562$, Figure 4B), or PCO_2 ($p = 0.375$, Figure 4C). Glucose was significantly higher ($p = 0.0312$, Figure 4D) and lactate was significantly lower ($p = 0.0156$, Figure 4E) in group C.

3.5 | Blood count

Blood counts (Figure 5) in groups C and R showed no significant difference in platelet count ($p = 0.0781$, Figure 5A), MPV ($p = 0.25$, Figure 5B), RBC count ($p = 0.6875$, Figure 5C), or MCV ($p = 0.375$, Figure 5D) between the two groups.

3.6 | TEG

TEG values (Figure 6) indicated that group C had significantly shorter R-HKH ($p = 0.0469$, Figure 6A), longer K-HKH ($p = 0.0156$, Figure 6B), lower MA-HKH ($p = 0.0312$, Figure 6C), higher MA-ActF ($p = 0.0156$, Figure 6D), and lower MA-HKH minus MA-ActF ($p = 0.0156$, Figure 6E) than group R. Group C also had significantly higher Aggregation-ADP ($p = 0.0156$, Figure 6F), consistent with the platelet aggregability data in Section 3.1. There was no significant difference for MA-ADP ($p = 0.0781$, Figure 6G).

4 | DISCUSSION

This study showed that 6-h cold storage of whole blood results in higher platelet aggregability and lower PF4, β-TG, and lactate levels compared to room temperature storage, without affecting P-selectin expression, platelet count, MPV, RBC count, and MCV. There have been previous reports of higher platelet aggregability and P-selectin expression after cold storage of whole blood or platelets for several days compared to storage at room temperature,[18–21] and of lower platelet counts when whole blood or platelet products are stored in the cold for several days compared to baseline[22,23] or to products stored at room temperature.[24,25] However, only one previous study has examined the effect of short-term storage on these parameters.[26]

The storage time of blood in ANH is a few hours, at most; therefore, a short storage time is needed to examine the optimal storage temperature in ANH, with an

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emphasis on platelet function. Thus, we set the storage time to 6 h, as in our previous study[27] of blood storage bags in ANH. The average anesthesia time for 3,407 non-emergent cardiac surgeries (surgery requiring cardiopulmonary bypass or an off-pump coronary artery bypass graft) at a single institution in the U.S. over a 3-year period was 440 min[28]; thus, the 6-h storage time is a reasonable estimate of that seen in practice.

The only previous comparison[26] of short-term cold and room temperature storage of whole blood, assuming use in ANH, found no significant difference in ADP-stimulated aggregability using rotational thromboelastometry (ROTEM). However, ROTEM is a whole blood assay that does not measure platelet function directly. The gold standard aggregation assay is the light transmission method using PRP[29] and the current study suggested higher aggregability after short-term cold storage using this method.

This study is the first to examine PF4 and β-TG in whole blood stored at cold or room temperature, and to examine P-selectin expression in whole blood stored for a short time at cold or room temperature. Platelets become activated during the preparation process and during prolonged storage.[10] PF4, β-TG, and P-selectin are present in the α granules of platelets, and since their expression increases with platelet activation, these proteins have long been recognized as markers of PSLs in transfusion medicine.[30] PSLs occur due to platelet metabolism,[15] and decrease platelet viability and hemostatic activity after transfusion and immunity.[15,30,31] Platelets are metabolically active and depend on adenosine triphosphate (ATP) hydrolysis for survival and function.[15] About 85% of ATP is produced by mitochondrial respiration in the tricarboxylic acid cycle (TCA).[15] However, the TCA is downregulated in the first three days of platelet storage, and glucose is exclusively converted to lactate via glycolysis,[32] which can cause PSLs.[33] Cold storage of platelets decreases basal respiration at rest and increases maximal respiration at activation.[34] That is, cold storage of platelets reduces metabolic demand, helps maintain mitochondrial function needed at activation, and suppresses PSLs. These events are consistent with our results. PF4 and β-TG are also referred to as platelet-derived cytokine.[35–37] Non-hemolytic reactions are one of the complications of platelet transfusions and are related to cytokine accumulation during storage of platelet products.[15] Our results for PF4 and β-TG suggest that cold storage reduces platelet-derived cytokine levels, resulting in better storage conditions.

Activated platelets change their shape and increase MPV,[38] and platelets with increased MPV produce large amounts of thromboxane A2, a prothrombotic factor, leading to thrombotic complications.[39] However, refrigeration of blood for several days did not significantly change MPV compared to baseline.[22,23] Therefore, it would be expected that short-term storage would have no effect, and our results are consistent with this expectation. Given that RBC products were refrigerated for several days, the adverse effects of cold storage on RBC-related parameters seemed unnecessary to consider, and we found no significant changes in RBC count and MCV after short-term storage.

For the HKH parameters in TEG, shortening of R and K and the increase of MA indicate hypercoagulability, but we did not obtain consistent results. MA-HKH minus MA-ActF, showing only the platelet contribution to clot strength, was significantly lower in group C than in group R, possibly because MA-ActF was significantly higher in group C. ActF contains factor XIII, as shown in Section 2.5.6. This supports the finding that cold platelets increase factor XIII expression in clots.[40] Aggregation-ADP increased in group C (>100% of group Pre), but decreased in group R (about 50% of group Pre). These results suggest that platelet aggregation via the ADP receptor, which decreases with storage at room temperature, may be enhanced rather than maintained in cold storage, and support the results for platelet aggregability in Section 3.1. However, given that the ADP channel in the PlateletMapping cartridge also contains factor XIII, the change in ADP parameters in TEG after cold storage might be due to increased factor XIII expression, rather than ADP receptors. This may also explain the increase in MA-ActF in group C. There have been no previous reports of the effects of cold storage on TEG 6s PlateletMapping parameters, and our results provide a basis for future research.

We did not examine the effect of 6-h storage on the platelet circulation time. The circulation time of cold-stored platelets is severely shortened, as noted in Section 1. However, in ANH during surgeries in which intraoperative bleeding or coagulation abnormalities occur, cold storage of blood with higher platelet aggregability may be effective, even at the expense of long-term platelet survival. The efficacy of cold platelet products in cases with bleeding is of increasing interest, and thus, our study of platelet function and hemostasis in ANH with comparison of cold and room temperature storage of autologous blood is of importance.

This study has several limitations. First, the measurements were performed in vitro, and it is unclear whether short-term cold storage of autologous whole blood in ANH improves hemostatic capacity after blood return and whether it reduces perioperative blood loss and use of allogenic transfusion products; hence, in vivo studies are needed in the future. Second, the storage time was fixed at 6 h. The actual storage time is determined by the

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progress of the surgery, and a change in storage time could lead to different results. Third, the PF4 and β-TG measurements and TEG did not use blood mixed with CPDA. Therefore, these results may differ for autologous blood stored in bags with CPDA for use in ANH. Fourth, the study of coagulation factors other than platelets was only conducted using TEG, and more detailed studies are needed for clinical application.

In conclusion, our results showed that 6-h cold storage of whole blood maintains higher platelet aggregability than room-temperature storage and provides better storage conditions for platelets. These results may help to determine the optimal method of short-term storage of fresh whole blood, including for ANH and especially for surgeries requiring rapid hemostasis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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