Clin. Lab. 2021;67:XXX-XXX


ORIGINAL ARTICLE

# Effects of Isovolumic Hemodilution and Platelet-Rich Plasma Separation on Platelet Activation State and Function, Complications, and Inflammation in Patients Undergoing Cardiac Surgery

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## SUMMARY

*Background:* **To explore the effects of isovolumic hemodilution and platelet-rich plasma separation on platelet activation state and function, complications, and inflammation in patients undergoing cardiac surgery.**
*Methods:* **A total of 80 patients who needed cardiac surgery under extracorporeal circulation from February 2018 to December 2019 in our hospital were selected as research subjects and divided into observation group (n = 40) and control group (n = 40) according to the random number table method. The patients in the observation group underwent platelet-rich plasma separation, while those in control group received acute isovolumic hemodilution. Then the platelet activation state and functional indexes, hemorheological indexes, and the coagulation functional indexes were compared between the two groups of patients before operation. Next, the changes in the levels of hemoglobin and high-sensitivity C-reactive protein (hs-CRP), an inflammatory factor, during blood protection (before and at 6 hours and 12 hours after intervention) were analyzed. Moreover, the dosage of blood products during operation was compared between the two groups, and postoperative complications and recovery in the two groups were statistically assessed.**
*Results:* **Before operation, the platelet adherence rate and aggregation rate in the observation group were significantly higher than those in control group ($p < 0.05$), while R and K values in thromboelastograms in the former were notably smaller than those in the latter ($p < 0.05$). Meanwhile, the whole blood low-shear viscosity, whole blood high-shear viscosity, and plasma viscosity in observation group were remarkably lower than those in control group ($p < 0.05$). In addition, the observation group exhibited shorter prothrombin time (PT), thrombin time (TT), and activated partial thromboplastin time (APTT) ($p < 0.05$) and a higher fibrinogen (Fib) level ($p < 0.05$) than the control group. At 6 hours and 12 hours after intervention and before operation, the hemoglobin level in observation group was markedly higher than that in control group ($p < 0.05$). In addition, the dosages of red blood cells, fresh frozen plasma, and platelets among blood products during operation in the observation group were evidently lower than those in the control group ($p < 0.05$), and the number of cases of hemorrhage, pulmonary infection, coagulation dysfunction, and paraplegia after operation in the former was distinctly smaller than that in the latter ($p < 0.05$). Furthermore, the observation group had an obviously smaller postoperative 24 hours drainage volume ($p < 0.05$) as well as shorter postoperative mechanical ventilation time and ICU treatment time than control group ($p < 0.05$).**
*Conclusions:* **For patients undergoing cardiac surgery under extracorporeal circulation, platelet-rich plasma separation and reinfusion technology can effectively ensure platelet activation state and function, reduce blood viscosity, ensure stable coagulation function, elevate hemoglobin level and decrease inflammatory reaction, and perioperative allogeneic blood infusion, with fewer adverse reactions in treatment, thus efficaciously facilitating the postoperative recovery of patients.**
**(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.200342)**

Manuscript accepted May 6, 2020

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## KEY WORDS

platelet-rich plasma separation, isovolumic hemodilution, extracorporeal circulation, platelet activation state and function, complication, inflammatory reaction


## INTRODUCTION

Cardiac surgery usually needs to be conducted under extracorporeal circulation, during which the surgery will negatively regulate the number and function of platelets, thereby leading to changes in the coagulation function and hemorheology of patients. All this will give rise to postoperative hemorrhage induced by non-surgical factors, thus affecting the operation result, and even threatening the life of patients [1]. Therefore, clinical patients undergoing cardiac surgery under extracorporeal circulation need the infusion of exogenous platelets, but large-dose allogeneic blood transfusion is highly risky with many complications. Therefore, autologous blood transfusion is mostly recommended in clinic, but the most practical and effective autologous blood transfusion method is still uncertain [2].

At present, acute isovolumic hemodilution is a method of autologous blood transfusion commonly used in clinical practice. A portion of blood of patients is drained to the outside of the body through storage after preoperative exsanguination, and then infused back into the body of the patients after extracorporeal circulation to avoid platelet damage caused by extracorporeal circulation during operation. This method can remarkably reduce the absolute blood loss during operation [3], but its protective effect on platelets is limited. In addition, hemodilution, electrolyte disturbance, and circulation overload may also occur during transfusion [4], which may lead to ischemia and anoxia of tissues and organs as well as heart failure when the body cannot compensate effectively. Platelet-rich plasma separation technology is a new type of autologous blood transfusion technology applied clinically in recent years. Platelet-rich plasma, pure plasma, and red blood cells are prepared by centrifuging autologous blood. Then the autologous blood can be reinfused into the body after extracorporeal circulation, thus efficaciously reducing the damage of the extracorporeal circulation to platelets, and preserving the number and function of platelets [5]. Meanwhile, the reinfused plasma and red blood cells can also retain coagulation factors of the body, so as to reduce the influence on coagulation function, improve the oxygen-carrying capacity of blood, and relieve ischemia reperfusion injury [6]. In this study, the effects of acute isovolumic hemodilution and platelet-rich plasma separation on platelet activation and function, complications, and inflammatory reaction in patients undergoing cardiac surgery under extracorporeal circulation were mainly explored.

## MATERIALS AND METHODS

### General data

A total of 80 patients admitted to our hospital from February 2018 to December 2019 who needed cardiac surgery under extracorporeal circulation were selected as research subjects. All patients signed the admission consent and applied for the approval of the Ethics Committee of the hospital before enrollment. Inclusion criteria: Patients aged 18 - 50 years old, those who were in grade II and/or III based on the American Society of Anesthesiologists (ASA) classification, and those whose hemodynamic indexes and respiratory function were stable, hemoglobin exceeded 120 g/L, and red blood cell volume exceeded 35%. Exclusion criteria: Patients who were treated with anticoagulant drugs or antiplatelet functional drugs within 7 days before admission, those whose platelet level was lower than 150 x $10^9$/L at enrollment, those who were classified into class IV based on the New York Heart Association (NYHA) Functional Classification, those whose left ventricular ejection fraction was lower than 55%, those with arrhythmia or pulmonary infection, those who refused to infuse allogeneic blood due to religious beliefs, or those who were allergic to the prepared drugs. These patients were divided into two groups, namely, observation group (n = 40) and control group (n = 40), using random number table method. In the observation group, there were 23 males and 17 females aged 18 - 50 years old, with an average of (46.5 ± 2.1) years old and body mass index of 21.5 - 26.0 kg/$m^2$. In terms of ASA classification, there were 21 cases of grade II and 19 cases of grade III. Besides, patients in this group received 45 - 90 (68.9 ± 5.3) minutes of extracorporeal circulation, and there were 35 cases complicated with hypertension, 21 cases complicated with coronary heart disease, 18 cases complicated with hyperlipidemia, and 17 cases complicated with chronic obstructive pulmonary disease. The control group consisted of 22 males and 18 females aged 18 - 50 years old, with an average of 46.6 ± 2.0 years old and body mass index of 21.6 - 26.1 kg/$m^2$. As for ASA classification, there were 20 cases of grade II and 20 cases of grade III. Patients received 45 - 90 (68.8 ± 5.2) minutes of extracorporeal circulation. In addition, there were 34 cases complicated with hypertension, 20 cases complicated with coronary heart disease, 19 cases of hyperlipidemia, and 18 cases complicated with chronic obstructive pulmonary disease. No statistically significant differences were detected in gender, age, body mass index, ASA grade, extracorporeal circulation time during operation, and the proportion of common internal diseases between the two groups ($p > 0.05$).

**Methods**

Blood protection technology was applied in all patients at 24 hours before operation. The control group underwent acute isovolumic hemodilution: Blood was collected via the elbow vein at a controlled speed of about 20 mL/minute, and the volume of the collected blood was controlled (over 90 g/L is generally proper) according to the patients' body mass, red blood cell level measured, and hematocrit value. Subsequently, hydroxyethyl starch and Ringer's lactate solution were infused to maintain stable circulation function. Then the collected whole blood was put into a blood collection bag containing sodium citrate, kept in a refrigerator at 4°C, taken out at 2 hours before operation for later use, and reinfused to the patients after extracorporeal circulation. In the observation group, the platelet-rich plasma separation technology was utilized at 24 hours before operation, and blood was collected via the elbow vein at a controlled speed of about 50 mL/minute, with hemoglobin of above 90 g/L. Next, hydroxyethyl starch and Ringer's lactate solution were infused to maintain stable circulation function. The collected autologous whole blood underwent platelet-rich plasma separation and was then introduced into a 55 mL centrifuge cup to prepare platelet-rich plasma, red blood cells, etc. Among them, red blood cells and platelet-poor plasma were infused back into the patients immediately after preparation, while platelet-rich plasma was kept in the refrigerator at 4°C, taken out at 2 hours before operation for later use and infused back into the patients after extracorporeal circulation.

**Observation indexes**

The platelet activation state and functional indexes, hemorheological indexes, and coagulation functional indexes were compared between the two groups of patients before operation. Next, the changes in the levels of hemoglobin and high-sensitivity C-reactive protein (hs-CRP), an inflammatory factor, during blood protection (before and at 6 hours and 12 hours after intervention) were analyzed. Moreover, the dosage of blood products during operation was compared between the two groups, and postoperative complications and recovery in the two groups were statistically assessed.

**Evaluation standard**

Platelet activation state and functional indexes included platelet adherence rate (glass microspherule rotation method, 29 - 40%), platelet aggregation rate (glass microspherule rotation method, normal value: 35 - 65%), reaction time in thromboelastograms (R value, normal reference value of whole blood: 10 - 16 minutes), and coagulation time (K value, normal reference value of whole blood: 5 - 10 minutes). Hemorheological indexes included changes in whole blood low-shear viscosity (8.23 - 9.57 mPa/second), whole blood high-shear viscosity (4.4 - 4.9 mPa/second), and plasma viscosity (1.65 - 1.95 mPa/second). Coagulation functional indexes included prothrombin time (PT, normal value: 11 - 13 second), activated partial thromboplastin time (APTT, normal value for male: 31.5 - 43.5 second and female: 32 - 43 second), thrombin time (TT, normal value: 16 - 18 second), and fibrinogen (Fib, normal value: 1.75 - 5.54 g/L). Besides, the inflammatory factor hs-CRP (< 10 mg/L) was mainly observed.

**Statistical processing**

SPSS 20.0 was adopted for statistical processing. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Comparison of the mean between two groups was conducted via *t*-test, and comparison of the rate between two groups was carried out via $\chi^2$ test. $p < 0.05$ indicated that the difference was statistically significant.

## RESULTS

**Comparisons of platelet activation state and functional indexes before operation**

The platelet adherence rate and aggregation rate before operation in the observation group were basically normal and significantly higher than those in the control group ($p < 0.05$). Additionally, R and K values in the thromboelastograms in the observation group were basically normal and remarkably lower than those in the control group ($p < 0.05$) (Table 1).

**Comparisons of hemorheological indexes between the two groups of patients before operation**

The hemorheological indexes whole blood low-shear viscosity, whole blood high-shear viscosity, and plasma viscosity in the observation group were markedly lower than those in control group ($p < 0.05$) (Table 2).

**Comparisons of coagulation functional indexes between the two groups before operation**

Among coagulation functional indexes, PT, TT, and APTT before operation in observation group were normal and shorter than those in control group, which were relatively prolonged. However, the level of Fib in the former was higher than that in the latter ($p < 0.05$) (Table 3).

**Changes in the hemoglobin level during blood protection**

Before intervention, at 6 hours and 12 hours after intervention, and before operation, the hemoglobin level was 13.3 ± 0.5 g/dL, 12.3 ± 0.5 g/dL, 13.0 ± 0.5 g/dL, and 13.4 ± 0.5 g/dL, respectively, in the observation group, and 13.4 ± 0.5 g/dL, 11.1 ± 0.3 g/dL, 10.6 ± 0.3 g/dL, and 9.8 ± 0.3 g/dL, respectively, in the control group,

**Table 1. Comparisons of platelet activation state and functional indexes before operation ($\bar{x} \pm s$).**

| | Platelet adherence rate (%) | Platelet aggregation rate (%) | R value (minutes) | K value (minutes) |
|---|---|---|---|---|
| Observation group | 35.2 ± 2.6 | 46.9 ± 3.9 | 12.3 ± 0.8 | 8.2 ± 0.3 |
| Control group | 23.6 ± 1.8 | 30.1 ± 1.0 | 17.9 ± 2.3 | 15.7 ± 1.9 |
| *t* | 23.200 | 26.391 | 14.544 | 24.660 |
| p | 0.000 | 0.000 | 0.000 | 0.000 |

**Table 2. Comparisons of hemorheological indexes between the two groups of patients before operation (mPa/s, $\bar{x} \pm s$).**

| | Whole blood low-shear viscosity | Whole blood high-shear viscosity | Plasma viscosity |
|---|---|---|---|
| Observation group | 9.8 ± 0.7 | 6.0 ± 0.1 | 1.5 ± 0.1 |
| Control group | 11.5 ± 1.5 | 6.9 ± 0.2 | 1.9 ± 0.2 |
| *t* | 6.495 | 25.456 | 11.314 |
| p | 0.000 | 0.000 | 0.000 |

**Table 3. Comparisons of blood coagulation function test results between the two groups before operation ($\bar{x} \pm s$).**

| | PT (second) | TT (second) | APTT (second) | Fib (g/L) |
|---|---|---|---|---|
| Observation group | 12.6 ± 1.3 | 17.6 ± 1.5 | 36.7 ± 1.8 | 2.7 ± 0.4 |
| Control group | 17.5 ± 2.1 | 23.1 ± 2.8 | 45.6 ± 2.5 | 1.3 ± 0.2 |
| *t* | 12.548 | 10.951 | 18.272 | 19.799 |
| p | 0.000 | 0.000 | 0.000 | 0.000 |

**Table 4. Dosage of blood products in the two groups during operation ($\bar{x} \pm s$).**

| | Red blood cell (U) | Fresh frozen plasma (mL) | Platelet (therapeutic dosage) |
|---|---|---|---|
| Observation group | 2.1 ± 0.1 | 300.5 ± 15.6 | 0.9 ± 0.2 |
| Control group | 4.2 ± 0.2 | 500.9 ± 28.9 | 2.3 ± 0.3 |
| *t* | 59.397 | 38.593 | 24.558 |
| p | 0.000 | 0.000 | 0.000 |

revealing that the hemoglobin level at the above time points in the observation group was notably higher than that in the control group ($t$ = 21.693, 30.370, and 11.926, $p = 0.000 < 0.05$) (Figure 1).

### Changes in the level of the inflammatory factor hs-CRP during blood protection

Before intervention, at 6 hours and 12 hours after intervention, and before operation, the hs-CRP level was 16.5 ± 1.3 mg/L, 8.3 ± 0.5 mg/L, 6.6 ± 0.3 mg/L, and 7.5 ± 0.4 mg/L, independently, in the observation group

**Table 5. Comparison of postoperative recovery between the two groups of patients ($\bar{x} \pm s$).**

| | Postoperative 24-hour drainage volume (mL) | Postoperative mechanical ventilation time (hour) | Postoperative ICU treatment time (d) |
|---|---|---|---|
| Observation group | 269.5 ± 25.3 | 20.9 ± 3.5 | 2.1 ± 0.2 |
| Control group | 386.7 ± 30.9 | 32.6 ± 5.9 | 3.2 ± 0.3 |
| *t* | 18.561 | 10.787 | 19.295 |
| p | 0.000 | 0.000 | 0.000 |

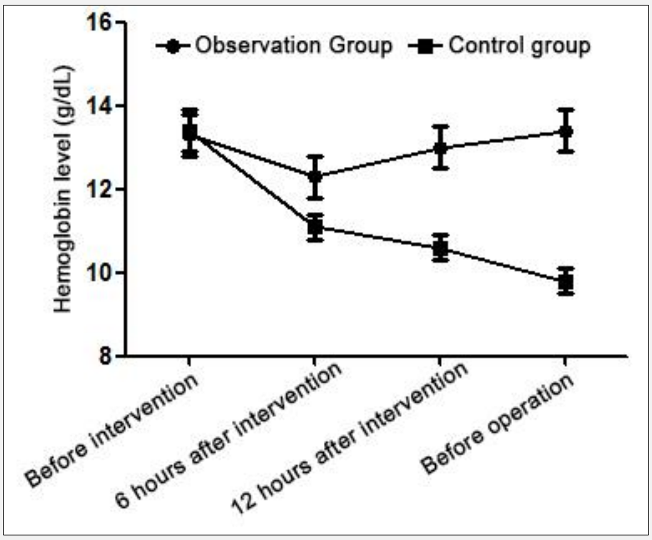


**Figure 1. Changes in the hemoglobin level during blood protection.**

and 16.6 ± 1.3 mg/L, 12.3 ± 0.9 mg/L, 10.8 ± 0.7 mg/L, and 11.9 ± 0.6 mg/L, independently, in the control group, reflecting that the hemoglobin level at the above time points in the observation group was evidently higher than that in the control group ($t$ = 24.572, 34.879, and 38.591, $p = 0.000 < 0.05$) (Figure 2).

**Dosage of blood products during operation in the two groups**

Dosages of red blood cells, fresh frozen plasma, and platelets among blood products during operation in the observation group were markedly smaller than those in the control group ($p < 0.05$) (Table 4).

**Comparisons of postoperative complications between the two groups**

After operation, there were 2 cases of hemorrhage, 1 case of pulmonary infection, no case of coagulation dysfunction, and no case of paraplegia in the observation group, with a total incidence rate of 7.5%, which was distinctly lower than that in the control group (50%) including 8 cases of hemorrhage, 6 cases of pulmonary infection, 5 cases of coagulation dysfunction, and 1 case of paraplegia ($\chi^2 = 15.622$, $p = 0.000 < 0.05$) (Figure 3).

**Comparison of postoperative recovery between the two groups of patients**

The observation group exhibited a remarkably lower 24-hour drainage volume ($p < 0.05$) and obviously shorter mechanical ventilation time and intensive care unit (ICU) treatment time after operation than the control group ($p < 0.05$) (Table 5).

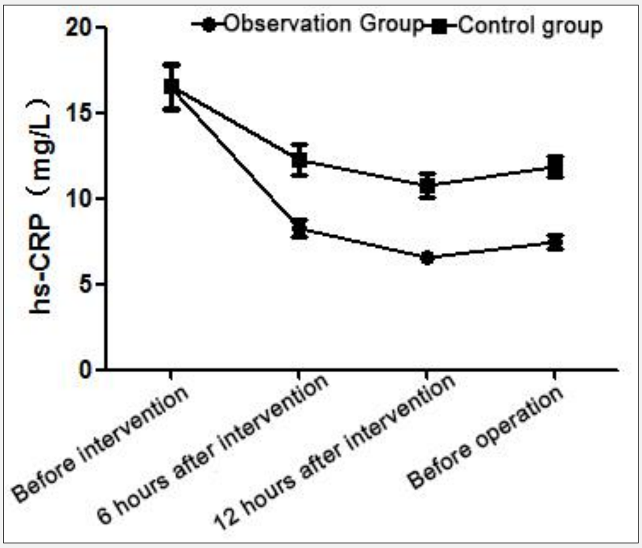


**Figure 2. Changes in the inflammatory factor hs-CRP level during blood protection.**

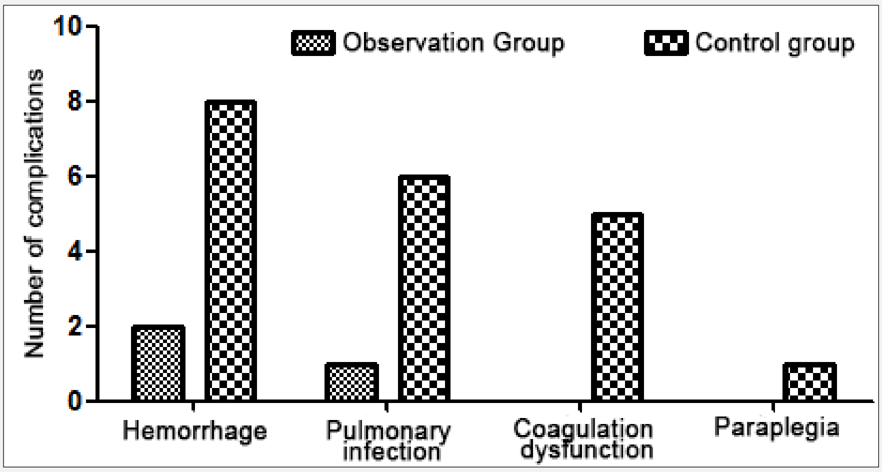


**Figure 3. Comparisons of postoperative complications between the two groups.**

## DISCUSSION

Extracorporeal circulation in cardiac surgery is a common cause of coagulation dysfunction after this surgery due to the reduction of platelets and dysfunction caused by foreign body contact. It is also an independent risk factor for postoperative hemorrhage resulting from non-surgical factors of patients [7]. As the medical level constantly advances in China, heart-related surgical treatment technology under extracorporeal circulation becomes more and more mature, but postoperative hemorrhage remains the major factor influencing the prognosis of patients [8]. Acute isovolumic hemodilution is a blood protection technology applied clinically in recent years. In this process, autologous bloodletting should be conducted at 1 day before operation or before heparinization, and fluid is infused to maintain circulation and stable blood physiological function at the same time. Extracorporeal circulation applied in patients undergoing cardiac surgery can reduce platelet damage, the destruction of plasma coagulation factors, and the amount of allogeneic blood transfusion after surgery to some extent [9]. However, acute isovolumic hemodilution has certain limitations in clinical application. For instance, it leads to the decreased coronary artery blood supply before operation and increased possibility of myocardial anoxia, and it may also give rise to decompensation and imbalance of oxygen supply and demand due to excessive hemodilution and hypohemoglobin [10]. Platelet-rich plasma separation technology can be utilized to effectively prepare blood component products mostly at 1 day before extracorporeal circulation, and the blood products are reinfused to the patients after extracorporeal circulation, which effectively reduces the loss of platelets and coagulation factors caused by extracorporeal circulation, thus reducing the amount of allogeneic blood transfusion after operation and improving the blood guarantee effect [11].

For patients undergoing cardiac surgery under extracorporeal circulation, acute isovolumic hemodilution was adopted in the control group, whereas platelet-rich plasma separation and reinfusion technology was employed in the observation group in this study. The platelet activation state and functional indexes before operation were compared between the two groups. It was found that the platelet adherence rate and aggregation rate among platelet activation state and functional indexes before operation in the observation group were basically normal and significantly higher than those in the control group. Additionally, R and K values in the thromboelastograms in the observation group were basically normal and remarkably lower than those in the control group. The above results suggest that platelet-rich plasma separation and reinfusion can efficaciously protect platelet function for patients undergoing cardiac surgery under extracorporeal circulation. Besides, hemorheological indexes before operation were compared between the two groups of patients, and the results manifested that the hemorheological indexes whole blood low-shear viscosity, whole blood high-shear viscosity, and plasma viscosity in the observation group were markedly lower than those in the control group, indicating that platelet-rich plasma separation and reinfusion technology can reduce blood viscosity to a certain degree in patients undergoing cardiac surgery under extracorporeal circulation. In the meantime, according to the comparison of coagulation functional indexes before operation between the two groups, among coagulation functional indexes, PT, TT, and APTT in the observation group before operation were normal and shorter than those, which were relatively prolonged, in the control group. However, the level of Fib in the former was higher than that in the latter. It can be seen that platelet-rich plasma separation and reinfusion technology can be applied to maintain the coagulation function of patients receiving cardiac surgery under extracorporeal circulation. Moreover, it was discovered from the comparison of the changes in the hemoglobin level during blood protection that the observation group exhibited a notably higher hemoglobin level than the control group before operation and at 6 hours and 12 hours after intervention. Meanwhile, the changes in the level of the inflammatory factor hs-CRP during blood protection was compared, the results of which demonstrated that the hemoglobin level in the observation group was distinctly higher than that in the control group before operation and at 6 hours and 12 hours after intervention. The above results imply that platelet-rich plasma separation and reinfusion technology is of positive significance for maintaining the hemoglobin level and reducing body inflammatory reaction in patients undergoing cardiac surgery under extracorporeal circulation. Subsequently, the dosage of blood products during operation was compared between the two groups. It was found that the dosages of red blood cells, fresh frozen plasma and platelets among blood products during operation in the observation group were markedly smaller than those in the control group, denoting that platelet-rich plasma separation and reinfusion technology is able to protect blood function and reduce the damage of extracorporeal circulation to platelets, plasma coagulation factors and red blood cells in patients undergoing cardiac surgery under extracorporeal circulation. And last, the postoperative complications were compared between the two groups, and the postoperative recovery was statistically assessed. According to the results, the total number of cases of postoperative hemorrhage, pulmonary infection, coagulation dysfunction, and paraplegia in the observation group was remarkably smaller than that in control group, and observation group had an evidently smaller 24-hour drainage volume as well as markedly shorter postoperative mechanical ventilation time and ICU treatment time than the control group. It can be seen that platelet-rich plasma separation and reinfusion can reduce perioperative complications and facilitate the postoperative recovery of patients undergoing cardiac surgery under extracorporeal circulation.

The acute isovolumic hemodilution method applied in the control group in this study avoids the damage of extracorporeal circulation through preoperative bloodletting, intraoperative infusion and preservation of a part of autologous blood components, especially platelets, coagulation factors, etc. [12], which is a relatively common perioperative autologous blood transfusion technology in cardiac surgery. However, the blood saving efficiency of this method needs to be improved, and such risks as organ ischemia and anoxia caused by excessive hemodilution and body decompensation exist [13]. Therefore, the platelet-rich plasma separation technology applied in the observation group in this study separates red blood cells, platelets, and plasma, which take up a large proportion in whole blood based on the centrifugation principle [14]; they are then stored separately [15] and reinfused to the body after extracorporeal circulation, thereby evidently reducing the damage to blood components caused by extracorporeal circulation, decreasing the activated polymorphonuclear neutrophils, and alleviating the immune response of the body and the systemic inflammatory reaction [16] after extracorporeal circulation. In the meantime, it can also reduce the influence of systemic heparinization on blood components to realize blood protection [17]. After transfusion of autologous platelet-rich plasma, this technology is able to efficaciously raise the number of platelets and the levels of Fib and related prothrombin in the body [18], reduce perioperative hemorrhage, and independently infuse red blood cells [19], so as to elevate the hemoglobin level of the body and reduce the possibility of complications caused by increased circulation load due to massive blood transfusion [20].

To sum up, for patients undergoing cardiac surgery under extracorporeal circulation, platelet-rich plasma separation and reinfusion technology can effectively ensure platelet activation state and function, reduce blood viscosity, ensure stable coagulation function, elevate hemoglobin level, and decrease inflammatory reaction and perioperative allogeneic blood infusion, with fewer adverse reactions in treatment, thus efficaciously facilitating the postoperative recovery of patients.

**Declaration of Interest:**

Authors declared no conflict of interests.

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