CLINICAL STUDY

Reduced Number of Platelets During Intra-Aortic Balloon Pumping Counterpulsation Predicts Higher Cardiovascular Mortality After Device Removal in Association with Systemic Inflammation

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Summary
Thrombocytopenia is a frequent complication in patients requiring intra-aortic balloon pumping (IABP) counterpulsation. However, its prognostic impact has not been fully addressed. The objective of this study is to evaluate the impact of the change in the platelet number during IABP use on the prognosis after device removal.

This is a retrospective observational study. Patients in the intensive cardiac care unit at three Juntendo University hospitals who underwent percutaneous implantation of IABP with or without veno-arterial extracorporeal membrane oxygenation (V-A ECMO), since 2012-2016, were enrolled in the study (n = 439). Patients who died during mechanical circulatory support (n = 47) were excluded. We evaluated the prognostic impact of the ratio of platelet reduction from the baseline (% PLT reduction) during IABP use on cardiovascular mortality after device removal.

The median and the range of follow-up period were 298 days and 0-1,869 days, respectively. Unadjusted Kaplan-Meier analysis demonstrated that patients with a higher % PLT reduction had higher cardiovascular (CV) mortality. An adjusted Cox proportional hazard analysis demonstrated that a 10% higher % PLT reduction was associated with higher cardiovascular (CV) mortality (Hazard ratio: 1.3, 95% Confidence interval: 1.1-1.6, P < 0.001). Moreover, % PLT reduction and the maximum C-reactive protein (CRP) level during IABP use were positively correlated (r = 0.326, P < 0.001).

The reduced number of platelets during IABP use was associated with an increased risk of CV mortality.

Key words: Platelet reduction, Cardiovascular death

Thrombocytopenia, generally defined as a low platelet count less than 150 × 10^9/L, has been demonstrated to be associated with an increased risk of adverse outcomes in patients with multiple contexts of cardiovascular disease, such as high in-hospital mortality rate in patients with acute coronary syndrome (ACS), higher all-cause mortality rate in heart failure patients, and high 1-year mortality after transcatheter aortic valve implantation (TAVI).

In hemodynamically unstable patients with critical cardiovascular disorders who require mechanical circulatory support, such as percutaneous placement of intra-aortic balloon pumping (IABP) counterpulsation, thrombocytopenia is one of the most frequent complications, with an incidence range of 20% to 60%. Thrombocytopenia in such patients has been thought to be primarily induced by the mechanical destruction of circulating platelets, and its prognostic impact for short-term adverse outcomes, such as in-hospital all-cause death, was previously described. Nevertheless, whether thrombocytopenia in patients with a mechanical circulatory support device predicts long-term cardiovascular events after its removal has not been adequately evaluated. Moreover, the underlying mechanism of the association between poor prognosis and thrombocytopenia in patients with IABP remains unclear.

This study was aimed at addressing the prognostic implications of thrombocytopenia during IABP use on cardiovascular mortality.
impact of the degree of reduction in platelet number during IABP counterpulsation with or without veno-arterial extracorporeal membrane oxygenation (V-A ECMO) in comparison with that before their induction on the incidence of cardiovascular mortality after device removal. To obtain a mechanistic insight into the possibility that thrombocytopenia under IABP use with and without V-A ECMO leads to a higher cardiovascular mortality rate, we evaluated the association between the extent of the reduction in platelet number and systemic inflammation during IABP counterpulsation.

Methods

Participants and follow-up duration: This is a retrospective observational study of a cohort consisting of consecutive 439 acutely critical patients who were using IABP with or without VA-ECMO during a hemodynamically critical condition during a 4-year period between January 2012 and December 2016 at three Juntendo University hospitals in Tokyo and Shizuoka Prefecture, Japan. The IABP types used in this study were a YAMATO/YAMATO Plus 7.5 French (Datascope, Fairfield, NJ) in 377 patients and a Corart BP sensor balloon 8 Fr (Senko Medical Instrument, Tokyo, Japan) in 62 patients. The V-A-ECMO device used in 71 patients was the Terumo emergency bypass system (Terumo Inc., Tokyo, Japan). Percutaneous IABP catheter insertion and cannulation of V-A ECMO catheters, if necessary, were performed by interventional cardiologists under fluoroscopic guidance.

All baseline data were obtained before the induction of IABP, the day of or 1 day before the induction. Patients who died during IABP use (n = 47) were excluded, and the remaining 392 patients were included in the baseline analysis. Patients without prognostic data (n = 10) were excluded from Kaplan-Meier and Cox proportional hazard analyses. The median and the range of the follow-up period after removal of the mechanical support were 298 days and 0-1869 days, respectively.

This study was approved by the institutional review board of Juntendo University School of Medicine and registered on the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) (ID: UMIN000007555). Written informed consent was obtained from all participants or from their representatives, when there was difficulty communicating with a participant. All participants were treated with intravenous administration of unfractionated heparin, and no one was diagnosed as having heparin-induced thrombocytopenia presenting the heparin platelet factor-4 (PF-4) antibody.

The endpoint evaluated in this study and its definition: The endpoint evaluated was whether cardiovascular mortality occurred in the follow-up period after IABP removal. Cardiovascular mortality was defined as death due to myocardial infarction, decompensated heart failure, critical arrhythmia, valvular heart disease, an aortic disease, peripheral artery disease, or sudden death, in which a non-cardiovascular cause could be excluded. During the follow-up period, all-cause death and cardiovascular death occurred in 69 (17.6%) and 63 (16.1%) patients, respectively. Among the 63 patients with cardiovascular mortality, 55 (87.3%) died within 100 days after removal of the mechanical circulatory support.

Definition, distribution and a cut-off value of percent platelet reduction during IABP counterpulsation (% PLT reduction): The baseline platelet number was measured prior to the induction of mechanical circulatory support. The minimum proportion of reduction in the platelet number during IABP use from the baseline platelet number was defined as percent platelet reduction (% PLT reduction), which was normally distributed and had median and mean values of 44.7% and 46.6%, respectively. In consideration with the clinical utility, we set the threshold of % PLT reduction as 50%, when we subdivided patients into two groups.

Statistical analysis: Continuous variables are presented as the mean ± standard deviation or median with interquartile range (IQR) in accordance with the results of the Shapiro-Wilk normality test, and they were compared using Student t-test or the non-parametric Mann-Whitney test. Categorical data are presented as numbers and percentages, and they were compared using the Fisher exact test. Unadjusted Kaplan-Meier curves for evaluation of the time to incidence of cardiovascular mortality were drawn and followed by the log-rank test for comparison of curves. Unadjusted univariate and adjusted multivariate Cox proportional hazard analyses for cardiovascular mortality were performed. A multivariate adjusted Cox proportional hazard analysis used three models with variables that were selected based on the univariate unadjusted analysis. Model 1 included the following covariates: age above 70 years, male sex, and % PLT reduction > 50. Model 2 included age above 70 years, male sex, small IABP size (30 mL), low systolic blood pressure (SBP) (< 102 mmHg, median) at presentation, use of both IABP and VA-ECMO, ACS, chronic kidney disease (CKD) defined as the estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m², longer IABP use (> 2.5 days, median), and % PLT reduction > 50. Model 3 included age of > 1 year, male sex, one size larger IABP, 10 mmHg higher in SBP, use of both IABP and VA-ECMO, ACS, 10 mL/minute/1.73 m² higher in eGFR, IABP use of > 1 day, and 10% higher in % PLT reduction. Correlations between two parameters were evaluated using Spearman’s non-parametric analysis. All probability values (P-values) were two-tailed and considered significant if less than 0.05.

Results

Background demographics (Table I) and platelet-related parameters in patients placed on mechanical circulatory support with or without % PLT reduction > 50: The background demographics and reasons for the mechanical circulatory support devices in all patients and those with or without % PLT reduction > 50 are listed in Table I. The most frequent cause of IABP induction was ACS (n = 184, 68.3%), and the second was support for high-risk PCI and cardiac surgery (n = 42, 10.7%). Concomitant use of V-A ECMO and IABP was needed in 43 patients (11.0%). The median and the interquartile range (IQR) in the duration of mechanical circulatory support...
device placement were 2.5 and 1.0-4.0 days, respectively. Patients with a % PLT reduction > 50 were more likely to be female and older and had lower body mass index (BMI), serum albumin, total cholesterol, triglyceride, and low density lipoprotein cholesterol (LDL-C) values. Impairment of renal and cardiac function, represented by low eGFR and elevated BNP, were more frequent in patients with % PLT reduction > 50. Baseline and peak C-reactive protein (CRP) levels (max. CRP) during mechanical circulatory support were substantially higher in patients with % PLT reduction > 50. The proportion of ST elevation myocardial infarction was lower in patients with % PLT reduction > 50, whereas those of cardiopulmonary arrest/ventricular fibrillation (CPA/VF) were similar in the groups with % PLT reduction ≤ 50 and > 50. Patients with higher % PLT reduction had higher cardiovascular mortality after device removal: Unadjusted Kaplan-Meier analysis with the log-rank comparison revealed significantly higher cardiovascular mortality in patients with % PLT reduction > 50 (26.3%) compared to those with % PLT reduction ≤ 50 (6.2%) (Figure 1A). Moreover, cumulative cardiovascular mortality in patients with % PLT ratio > 70% was markedly higher compared to those in patients with % PLT ration of 30%–50% and < 30% (Figure 1B). Furthermore, patients who received platelet transfusion had a higher cardiovascular mortality rate in the group of % PLT reduction > 50, whereas cardiovascular mortality was similar in the group with % PLT reduction ≤ 50 (Supplemental Figure 1).

### Table 1. Baseline Demographics of Patients with or without a Decrease in the Number of Platelets During IABP Support, Compared to the Baseline Number of Platelets (% PLT Reduction)

| Factors                        | All n = 392 | % PLT reduction ≤ 50 n = 232 | % PLT reduction > 50 n = 160 | P-value |
|--------------------------------|-------------|-------------------------------|-------------------------------|---------|
| Gender, male                   | 301, 76.8%  | 189, 81.8%                    | 112, 70.0%                    | 0.007   |
| Age, years old                 | 70.3 ± 11.6 | 69.4 ± 11.4                   | 71.6 ± 11.9                   | 0.064   |
| BMI                            | 23.1 ± 4.0  | 23.5 ± 3.9                    | 22.5 ± 4.0                    | 0.023   |
| Systolic BP, mmHg              | 103.2 ± 31.0| 107.4 ± 30.6                  | 97.0 ± 30.6                   | 0.001   |
| HR, beats per minute           | 87.7 ± 24.0 | 86.5 ± 22.5                   | 89.4 ± 25.9                   | 0.249   |
| Alb mg/dL                      | 3.7 (3.2-4.0)| 3.8, (3.2-4.1)                | 3.6 (3.1-4.0)                 | <0.001  |
| Total cholesterol, mg/dL       | 178.3 ± 52.4| 187.5 ± 55.3                  | 164.3 ± 44.4                  | <0.001  |
| Triglycerides mg/dL            | 80.5 (56.0-129.0) | 90.5, (61.8-140) | 73.5 (50.3-116) | 0.003   |
| LDL-C mg/dL                    | 106.7 ± 41.5| 114.4 ± 44.7                  | 95.4 ± 33.4                   | <0.001  |
| BNP pg/mL                      | 196.3 (47.0-624.4) | 142.1 (38.9-408.0) | 332.1 (88.7-1351.6) | <0.001  |
| Hb g/dL                        | 12.6 ± 2.4  | 12.8 ± 2.3                    | 12.3 ± 2.4                    | 0.057   |
| Creatinine, mg/dL              | 0.96 (0.74-1.4)| 0.9 (0.73-1.3) | 1.0 (0.76-1.8) | 0.023   |
| eGFR, mL/minute/1.73 m²        | 56.2 ± 30.0 | 59.9 ± 29.3                   | 50.7 ± 30.2                   | 0.003   |
| CKD                            | 204, 52.2%  | 106, 45.9%                    | 98, 62.0%                     | 0.002   |
| Baseline CRP, mg/dL            | 0.4 (0.3-2.1)| 0.3 (0.3-1.5)                 | 0.5 (0.3-2.9)                 | 0.018   |
| Peak CRP during IABP support, mg/dL | 14.2 (9.0-20.1) | 11.9 (7.0-18.0) | 16.5 (12.8-21.5) | 0.039   |
| STEMI*                         | 184, 46.9%  | 120, 51.7%                    | 64, 40.0%                     | 0.02    |
| NSTEMI/UAP†                    | 84, 21.4%   | 50, 21.6%                     | 34, 21.3%                     | 0.13    |
| Support of CV surgery/PCT‡     | 42, 10.7%   | 20, 8.6%                      | 22, 13.8%                     | 1.00    |
| CHF‡                           | 32, 8.2%    | 13, 5.6%                      | 19, 11.9%                     | 0.04    |
| CPA/VF**                       | 22, 5.6%    | 14, 6.0%                      | 8, 5.0%                       | 0.82    |
| Others                         | 28, 7.1%    | 15, 6.5%                      | 13, 8.1%                      | 0.55    |
| IABP duration                  | 2.5 (1.0-4.0)| 2.0 (1-3)                     | 3.0 (2-5.75)                  | <0.001  |
| IABP size, mL                  | 35.7 ± 3.6  | 36.0 ± 3.6                    | 35.3 ± 3.7                    | 0.04    |
| Use of V-A ECMO                | 43, 11.0%   | 9, 3.9%                       | 34, 21.4%                     | <0.001  |
| Baseline Platelet No., × 10^9/L| 200.4 ± 70.6| 198.0 ± 65.5                  | 203.8 ± 77.6                  | 0.42    |
| Minimum Platelet No., × 10^9/L | 105.4 ± 51.5| 130.8 ± 45.2                  | 68.6 ± 35.3                   | <0.001  |
| Days until minimum Platelet No.| 2.3 ± 1.5   | 1.9 ± 1.2                     | 2.8 ± 1.8                     | <0.001  |
| Mean platelet volume, fL       | 9.3 ± 1.5   | 9.2 ± 1.4                     | 9.5 ± 1.6                     | 0.042   |
| Platelet distribution width, fL| 12.5 ± 2.3  | 12.4 ± 1.9                    | 12.7 ± 2.6                    | 0.13    |
| Platelet transfusion           | 77, 20%     | 13, 5.6%                      | 64, 40.5%                     | <0.001  |

* ST-elevation myocardial infarction. § Non-ST-elevation myocardial infarction/unstable angina. ‡ Cardiovascular surgery/percutaneous.

Increased risk of cardiovascular mortality after IABP removal in patients with reduced platelet number (% PLT reduction) during IABP counterpulsation: An adjusted Cox proportional hazard analysis using three different models was used to evaluate prognostic impact of % PLT reduction on higher cardiovascular mortality. In these models, % PLT reduction > 50 was included as a nominal variable in Models 1 and 2, and 10% higher of % PLT reduction was used in Model 3. As presented in Table II and the Supplemental Table, the multivariate...
Cox proportional hazard analysis continuously demonstrated the prognostic impact of % PLT reduction on cardiovascular mortality. In Models 1 and 2, % PLT reduction > 50 was an independent risk factor for cardiovascular death after IABP removal (first and second rows in Table II and Supplemental Table). By contrast, 10% higher in % PLT reduction as a continuous variable was significantly associated with elevated cardiovascular death (34% relative risk elevation) (third row in Table II and Supplemental Table). Moreover, the elevated risk of higher % PLT reduction for CV mortality was independent of platelet transfusion (Supplemental Table), although there was a significantly higher cumulative CV mortality rate in patients who received platelet transfusion with % PLT reduction > 50 (Supplemental Figure 2).

Receiver operating characteristic (ROC) curves and their C-statistics of % PLT reduction for predicting cardiovascular mortality: To test the accuracy and cut-off levels of % PLT reduction in predicting cardiovascular mortality, a ROC curve was prepared. The measured C-statistics of % PLT reduction was 0.761. The cut-off values of % PLT reduction for predicting cardiovascular mortality was calculated to be 56.3%, using the Youden index. At that cut-off value % PLT reduction, the specificity, sensitivity, and positive and negative predictive values were 0.79, 0.65, 0.69 and 0.75, respectively (Figure 2). These findings indicate that accuracy of % PLT reduction in prediction of cardiovascular mortality in patients required IABP with or without V-A ECMO.

Unfavorable prognostic impact of higher % PLT reduction during IABP counterpulsation in various subgroups: Multivariate Cox proportional hazard analysis calculated hazard ratios of 10% higher % PLT reduction for predicting cardiovascular mortality in various subgroups (Supplemental Figure 1). In this analysis, a multivariate Cox proportional hazard analysis using a model that included age, sex, and 10 higher % PLT reduction (as a continuous variable) except for the subclasses of females/males older than 70 years or younger. As a result, higher % PLT reduction was continuously associated with a significantly elevated risk of cardiovascular mortality in all subpopulations, such as females and males, ≤70- and >70-years-old, SBP > and ≤121 mmHg (median), with and without diabetes and CKD, BMI > and ≤22.7, and with or without ACS.

A correlation between % PLT reduction and maximum C-reactive protein (CRP) during IABP counterpulsation: The correlation between % PLT reduction and the maximum CRP level (max. CRP) as a surrogate for the degree of systemic inflammation during IABP use was evaluated. A significant positive correlation between % PLT reduction and max. CRP level was observed (r = 0.326, P < 0.001) (Figure 3). These data suggest some role for inflammation in the reduction in platelet number in patients with IABP counterpulsation.

Discussion

This study demonstrated that the greater reduction in the number of platelets during IABP counterpulsation was independently associated with an increased risk of death due to a cardiovascular cause after IABP removal. The multivariate Cox proportional hazard analysis indicated the elevated risk of platelet reduction during IABP use for cardiovascular mortality was independent from platelet transfusion. Moreover, a significant role of inflammation, represented by an elevated level of CRP during IABP use, was postulated, although the pathophysiology of this association still warrants exploration.

Low platelet count or thrombocytopenia, generally defined as platelet number less than 150 × 10^9/L, has been previously demonstrated to be a marker of adverse outcomes in patients in the intensive care unit (ICU) and in those with multiple cardiovascular diseases. In ACS pa-
thrombocytopenia are complicated in each case, the disease represents either increased destruction/consumption or decreased production of platelets. A previous study indicated that chemokines including the vascular endothelial growth factor and Regulated on Activation Normal, T-cell Expressed and Secreted increased after TAVI, which may reflect platelet activation.\cite{30}

Percutaneously implanted mechanical circulatory support devices have progressively become an effective therapeutic option in critical patients with cardiovascular diseases, typically those with cardiogenic shock, and in the setting of high-risk interventions.\cite{29,30} There has been substantial technological progress in this field, including IABP, V-A or V-V ECMO, the CentriMag pump, and temporary ventricular assist devices such as Tandemheart and the Impella system. Among these, IABP is the most widely used compared to the other devices since it has lower risks during placement, is less invasive and easy to use, and may be a first-line mechanical circulatory support option, despite the controversies regarding its efficacy in the setting of cardiogenic shock.\cite{30} In this study, IABP was used in all patients and together with V-A ECMO in 11.0% of the patients, because these were the only two devices available in Japan during the study period of 2012-2016. Further evaluation may be needed to address whether the findings in this study can be applicable to patients with mechanical circulatory support devices other than IABP and V-A ECMO.

**Table II. Adjusted Multivariate Cox Proportional Hazard Analyses Regarding % PLT Reduction on Cardiovascular Mortality Using Three Models**

| Model | HR     | 95% CI  | P-value |
|-------|--------|---------|---------|
| Model 1* (a nominal variable, % PLT reduction > 50%) | 3.3 | 1.9-5.6 | <0.001 |
| Model 2† (a nominal, % PLT reduction > 50%) | 1.9 | 1.1-3.5 | 0.04 |
| Model 3‡ (a continuous variable, 10% higher in %PLT reduction) | 1.3 | 1.1-1.6 | <0.001 |

* Model 1 includes the elderly (> 70 years old), male gender and % PLT reduction > 50%. † Model 2 includes the elderly (> 70 years old), male gender, small IABP size (30 mL), low SBP (< 102 mmHg, median), use of V-A-ECMO and IABP, ACS, CKD, IABP use for a long time and % PLT reduction > 50%. ¶ Model 3 includes 1 year older, male gender, a larger IABP, 10 mm Hg higher SBP, use of V-A-ECMO and IABP, ACS, 10 mL/minute/1.73 mm² higher eGFR, a day longer IABP use, and 10% higher % PLT reduction.

**Figure 2.** Receiver operating characteristic (ROC) curves of % PLT reduction during IABP support for cardiovascular mortality. C-statistics of the ROC curve indicate moderate to high accuracy of % PLT reduction for predicting cardiovascular mortality. The cut-off value of % PLT reduction was 56.3%. The cut-off value, sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of % PLT reduction were 0.79, 0.65, 0.69 and 0.75, respectively.

**Figure 3.** Correlation between % PLT reduction and the maximum serum CRP (max. CRP) level during IABP counterpulsation. The correlation coefficient between max. CRP and % PLT reduction was 0.326, indicating a moderate correlation between these two parameters (P < 0.001).
A growing body of evidence indicates that platelets play a crucial role in local and systemic inflammation in many pathological settings, such as dermatitis, arthritis, glomerulonephritis, sepsis and extensive atherosclerosis, by mediating recruitment of inflammatory cells. The release of proinflammatory factors and cytokines by platelets is also central to promotion of inflammation. The activation and apoptosis of platelets promotes membrane vesiculation and platelet-derived microparticle release. Platelet-delivered microparticles are known to be associated with inducing inflammation via CD40/40L and IL-1 pathways, as well as progression of atherosclerosis. There is a report demonstrating that platelet-derived microparticles enhance C-reactive protein. In this study, a moderate but significant positive correlation between % PLT reduction and max. CRP during IABP counterpulsation was demonstrated, indicating that patients with more severe thrombocytosis had higher systemic inflammation. Although the precise mechanisms explaining this inverse correlation are yet to be clarified and none of the serum platelet-derived proinflammatory factors or cytokines have been measured, it may be possible that the mechanical destruction and apoptosis of platelets through mechanical circulatory support devices may induce the release of proinflammatory factors by platelets, resulting in promotion of systemic inflammation.

**Limitations of the study:** This study has several limitations. First, it is a retrospective study, which can identify correlations, but it was not designed to establish causality. Therefore, the underlying mechanism findings in this study need to be further evaluated, although a possible role for inflammation in the adverse outcomes was implied. Second, this study did not primarily investigate hematological or other causes of the reduction in the platelet number during IABP use, such as bone marrow insufficiency for platelet production, excessive thrombotic status (such as microangiopathy (TMA) and DIC), and severe liver or kidney dysfunction. Third, the mechanical support devices used in this study were limited to IABP and V-A ECMO. Therefore, further investigations are required before we can generalize the findings in this study to patients using other mechanical circulatory support devices.

**Conclusions**

The findings in this study indicate the utility of the ratio of reduced platelet number as a prognostic indicator in patients using IABP for predicting higher cardiovascular mortality. The role of systemic inflammation during IABP counterpulsation was suggested as one of the potential underlying mechanisms of the association between thrombocytopenia and poor cardiovascular outcomes. The earlier removal of IABP may need to be considered in patients with greater reduction of platelet number under IABP counterpulsation.

**Disclosure**

Conflicts of interest: All authors have nothing to disclose.

**Ethics approval and consent to participate:** This study was approved by the institutional review board of Jun-tendo University School of Medicine and registered on the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) (ID: UMIN000007555). Written informed consent was obtained from all participants or their representatives, when there was difficulty communicating with a participant.

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**Supplemental Files**
Supplemental Table
Supplemental Figures 1, 2
Please see supplemental files; https://doi.org/10.1536/ihj.19-349