Post-Cardiotomy Pericardial Effusion and Postoperative Atrial Fibrillation Risk

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Abstract

Purpose

Postoperative atrial fibrillation is a poor prognostic factor that increases mortality rates. We have observed that patients who experienced significant pericardial effusion developed postoperative atrial fibrillation; however, little research has been conducted examining the association between postoperative atrial fibrillation and post-cardiotomy pericardial effusion.

Methods

This retrospective, single-center study included adult patients who underwent cardiovascular surgery via median sternotomy from January 2016 to December 2019. Patients who underwent routine postoperative computed tomography at 7±3 days after surgery (n = 294) were included. Pericardial effusion was measured at its thickest point. Patients were classified into groups with (n = 127) and without (n = 167) postoperative atrial fibrillation, and the association of pericardial effusion with other factors was evaluated. A possible confounder adjusted logistic regression analysis after multiple imputation was performed to obtain odds ratios for postoperative atrial fibrillation using previously published risk factors.

Results

Age, intraoperative bleeding volume, and pericardial effusion size were all significantly higher in the group with postoperative atrial fibrillation. Multivariate logistic regression after multiple imputation revealed that age, intraoperative bleeding volume, and postoperative pericardial effusion were significantly associated with postoperative atrial fibrillation.

Conclusion

To our knowledge, this is the first study focusing on the relationship between post-cardiotomy pericardial effusion and postoperative atrial fibrillation. Our findings showed that post-cardiotomy pericardial effusion is associated with postoperative atrial fibrillation. However, causality remains unknown, making further studies mandatory.

Introduction

Postoperative atrial fibrillation (POAF) is a common complication after cardiovascular surgery.[1-5] Several reports have defined the pathogenesis of POAF, but some clinical associations remain poorly characterized. The risk factors for POAF have been previously reported as *preoperative* predictors (age, male sex, history of atrial fibrillation, congestive heart failure, arterial hypertension, obesity, white ethnicity, and chronic obstructive pulmonary disease), *perioperative* (intraoperative) predictors (mitral valve surgery, intra-aortic balloon pump, cross-clamp time, bicaval cannulation, and venting via pulmonary vein), and *postoperative* predictors (pneumonia, respiratory events [ventilation for >24 hours and respiratory insufficiency], inotropic drug use, and atrial pacing). Dobrev et al. reported a conceptual

model of POAF that included temporal development of the components of a vulnerable substrate to determine when and where these risk factors have their effect. In their report, they separated risk factors into the three groups *pre-existing atrial substrate*, *surgery-induced substrate*, and *transient postoperative factors*. We hypothesized that the transient postoperative factors listed in the report were likely important for preventing POAF because they are treatable components.[6] Similarly, we have observed POAF in numerous patients with significant pericardial effusion (PE). There has been little research correlating PE and POAF. We aimed to determine the extent of PE in patients who experienced POAF compared to that of patients with uneventful postoperative courses, with the hypothesis that PE would be more common and extensive in patients with POAF.

Methods

Patient selection

Data from 750 consecutive patients who underwent cardiovascular surgery from January 2016 to December 2019 in our department were retrospectively analyzed. Due to the study's retrospective design, the requirement for informed patient consent was waived. The study was approved by the Institutional Review Board of Asahikawa Medical University.

Adult patients who underwent cardiac surgery via median sternotomy were included, and those with preoperative atrial fibrillation, pre/postoperative placement of pacemaker or implantable cardioverter-defibrillator, minimally invasive surgery, and cases without median sternotomy were excluded.

We evaluated PE using computed tomography (CT) at 7±3 days postoperatively, and patients who lacked a CT scan at that time were excluded. The thickest portion of the PE was measured (Fig. 1).

Following exclusions, 294 patients were enrolled and classified into groups with (POAF+ group; n = 127) and without (POAF− group; n = 167) POAF (Fig. 1). We also analyzed the number of patients in each of the CHA_2DS_2-VASc score levels developed by Chua et al. as a potential predictor of POAF.[7] The CHA_2DS_2-VASc items include congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular (coronary) disease, age 65-74 years, and sex (female). Each item present is scored as 1 point, except age ≥75 years and stroke/TIA, which are scored as 2 points, and the highest possible score is 9.

Statistical analyses

Normal distribution of continuous variables was determined using the Kolmogorov-Smirnov test. Some variables failed the normality test and were therefore analyzed using the Mann-Whitney U test and are reported as median with interquartile range (IQR). Categorical variables were compared using Fisher's exact test. Univariate analysis was performed to compare the preoperative characteristics, operative data, and postoperative outcomes/findings between the POAF+ and POAF− groups. For further evaluation, we

conducted multivariate logistic regression analysis with explanatory variables of age, sex, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, vascular disease, stroke or TIA, operative procedure (coronary artery bypass grafting, valve surgery, aortic surgery), intraoperative bleeding, and postoperative pericardial effusion, which are previously reported POAF risk factors.[3-6,8,9] Missing data were managed with multiple imputation by chained equations using the above mentioned outcomes and explanatory variables. Twenty-five datasets were imputed with 10 iterations each. We also evaluated the correlation between intraoperative bleeding volume and PE using Spearman's rank correlation coefficient.

Statistical analyses were conducted using EZR 2.7 (Saitama Medical Center, Jichi Medical University, Japan). Multiple imputation and logistic regression analyses were performed with mice package in the R software program, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Preoperative patient characteristics are shown in Table 1. Patients in the POAF+ group were significantly older than those in the POAF– group (76 years, range: 68-80 years vs. 68 years, range: 56-75 years, p<0.001). All other patient characteristics were similar between the groups.

Intraoperative data are shown in Table 2. The intraoperative bleeding volume was significantly higher in the POAF+ group than in the POAF– group (23.6 dL, range: 10.2-42.5 dL vs 16.7 dL, range: 9–31.5 dL, p=0.029). The aortic surgery was significantly lower in the POAF+ group than in the POAF– group (40 [31.5%] vs. 76 [45.5%], p=0.016).

Postoperative outcomes (Table 3) revealed that the average PE thickness was 8.5 (range, 0-15.8) mm in the POAF+ group and 0 (0-9.3) mm in the POAF– group (p<0.001) (Fig. 2). There were several outliers in the POAF– group, but these did not appear to affect the statistical analyses.

Multivariate logistic regression analysis results after multiple imputation are shown in Table 4. There were significant differences in age (OR, 1.07; 95% CI, 1.04-1.10; p<0.001), intraoperative bleeding volume (OR, 1.02; 95% CI, 1.00-1.03; p=0.002), and postoperative PE (OR, 1.04; 95% CI, 1.01-1.08; p=0.006), indicating that these are significantly associated with POAF. There was also a significant difference in aortic surgery (OR, 0.44; 95% CI, 0.22-0.88; p=0.019), suggesting that this is negatively associated with POAF. There was also a statistical correlation between intraoperative bleeding volume and PE (Spearman's rank correlation rho=0.137, p=0.0196), though the correlation was weak and did not reach statistical significance (Fig. 3).

Discussion

Dobrev et al. reported a conceptual model of POAF and indicated influences of pre-existing atrial substrate, surgery-induced substrate, and transient postoperative factors.[6] In this study, we focused on

post-cardiotomy PE and hypothesized that the presence of PE correlates with transient postoperative factors. One cause of PE is postoperative bleeding or inflammation of the pericardium.[10] Moreover, pericardial inflammation causes POAF. Although PE and POAF are both consequences of inflammation, the correlation between PE and POAF in this context has not been reported. The results of this study highlight the association between PE and POAF and support the idea that assessing cytokines, inflammation, and oxidative stress markers in PE will be helpful in understanding the mechanisms of POAF. Olesen et al. supported this principle in reporting a correlation between serum C-reactive protein level, which is an inflammatory marker, and the occurrence of POAF in patients who underwent coronary artery bypass grafting.[11] However, they did not specify the cause of inflammation.

Imazio et al. reported the effects of colchicine on POAF.[12] Although they concluded that colchicine did not prevent POAF or reduce postoperative PE in postpericardiotomy syndrome, there was no consideration of the extent of PE in these patients. The cause of POAF in that study was potentially a combination of inflammation and mechanical stress to the heart due to PE. Mechanical stress caused by PE may affect the autonomic nervous system (ANS),[13] which is also a transient postoperative factor associated with POAF. Congestive cardiac tamponade due to PE activates the renin-angiotensin-aldosterone system and leads to ANS activation. ANS activation is essential to understanding POAF because several reports observed that β-blockers were effective for prevention and treatment of POAF. If this hypothesis is correct, extending the time of tube drainage from the cardiac sac after surgery may be effective in reducing the prevalence of POAF. However, there is another hypothesis that PE is secondary to POAF. Atrial fibrillation may precipitate congestive heart failure, which may lead to accumulation of pericardial fluid.[14, 15] Thus, the findings of this study are insufficient for concluding the cause-and-effect relationship between PE and POAF.

Our study also indicated that intraoperative bleeding volume was a positive predictor of POAF, despite the lack of a clinically significant relationship between intraoperative bleeding and PE. This could suggest that patients who experienced significant intraoperative bleeding were transfused with blood derivatives, which can trigger a cytokine storm and cause POAF.

Conversely, aortic surgery was a significant negative predictor of POAF in our study, despite having higher intraoperative bleeding volumes. Eikelboom et al. reported that POAF occurred more frequently after CABG and valve surgery.[16] These conclusions also supported the induction of myocardial ischemia and structural remodeling of the atrium by mechanical stress associated with incisions, leading to POAF.[6] Additionally, a previous report observed that cardiopulmonary bypass time affected the occurrence of POAF,[17] but we did not observe a statistical difference. The number of patients who underwent CABG in this study was low because they underwent postoperative CT scans within 2-3 days after surgery and were therefore excluded. Therefore, it is difficult to make conclusions about the effects of CABG on POAF.

The occurrence of POAF despite the administration of β-blockers indicates that POAF can develop secondary to changes in ANS activity, inflammation, or myocardial ischemia and highlights the importance of risk reduction. Effective drainage of PE has the potential to reduce inflammation in the

cardiac sac and may subsequently decrease the occurrence of POAF. Further studies on this topic have the potential to reveal additional treatment options for POAF.

This study had several limitations. The single-center, retrospective cohort design using electronic charts could have introduced information bias. Additionally, PE thickness was calculated manually from CT images, making the measurements slightly subjective. However, these measurements were taken before we investigated POAF occurrence, which limited observer bias.

Conclusions

This study suggests that age, intraoperative bleeding volume, and postoperative PE are positive predictive factors of POAF. The results also suggest that aortic surgery is a negative predictive factor. However, the causal association between PE and POAF remains unclear. Further studies are needed to confirm the role of PE in POAF, such as biochemical testing of pericardial fluid. This could help in understanding the mechanisms behind POAF.

Declarations

Funding:

None

Conflicts of interest:

The authors have no conflicts of interest directly relevant to the content of this article.

Ethics aprooval:

The study was approved by the Institutional Review Board of Asahikawa Medical University. Date: 20. April. 2021, Approval Number: 20107

Informed consent:

Owing to the retrospective design, the requirement for informed patient consent was waived.

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Tables

Table 1. Preoperative characteristics

Preoperative characteristics

	All patients		Missing	POAF+	POAF–	p value
	n = 294		n, (%)	n = 127 (%)	n = 167 (%)	
Age, y median (IQR)	71 (62-79)		0	76 (68-80)	68 (56-75)	**< 0.001**
male	176 (59.9)		0	73 (57.5)	103 (61.7)	0.474
Hypertension	208 (70.8)		0	92 (72.4)	116 (69.5)	0.607
Diabetes Mellitus	80 (27.2)		0	39 (30.7)	41 (24.6)	0.29
COPD	25 (8.5)		0	10 (7.9)	15 (9.0)	0.834
Chronic kidney disease	75 (25.5)		0	33 (26.0)	42 (25.1)	0.893
Chronic heart failure	29 (9.9)		1 (0.3)	15 (11.8)	14 (8.4)	0.43
Vascular disease	115 (39.1)		23 (7.8)	50 (39.4)	65 (38.9)	1
Stroke or TIA	42 (14.3)		23 (7.8)	24 (18.6)	18 (10.8)	0.061
Preoperative ACS	30 (10.2)		0	10 (7.9)	20 (12.0)	0.331
Preoperative antiplatelet	96 (32.7)		0	39 (30.7)	57 (34.1)	0.616
Preoperative anticoagulant	18 (6.1)		0	76 (59.8)	11 (6.6)	0.809
Redo surgery	24 (8.2)		0	8 (6.3)	16 (9.6)	0.391
CHA_2DS_2-VASc score	median (IQR)	3 (2-5)	23 (7.8)	4 (2-5)	3 (2-4)	0.182
	0	15 (5.1)		8 (4.8)	7 (5.5)	
	1	29 (9.9)		15 (9.0)	14 (11.0)	
	2	46 (15.7)		30 (18.0)	16 (12.6)	

3	51 (17.4)	34 (20.4)	17 (13.4)	
4	59 (20.1)	32 (19.2)	27 (21.3)	
5	45 (15.3)	25 (15.0)	20 (15.7)	
6	15 (5.1)	7 (4.2)	8 (6.3)	
7	10 (3.4)	2 (1.2)	8 (6.3)	
8	1 (0.3)	1 (0.6)	0 (0)	

Abbreviations: POAF, postoperative atrial fibrillation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; ACS, acute coronary syndrome

Table 2. Intraoperative data

Intraoperative data						
		All patients	Missing	POAF+	POAF-	p value
		n = 294	n, (%)	n=127 (%)	n=167 (%)	
Operative procedure	CABG	60 (20.4)	0	27 (21.3)	33 (19.8)	0.772
	Valve	115 (39.1)	0	44 (34.6)	71 (42.5)	0.186
	Aorta	116 (39.5)	0	40 (31.5)	76 (45.5)	**0.016**
	others	41 (14.0)	0	18 (14.2)	23 (13.8)	1
Intraoperative bleeding, dL (IQR)		18.7 (9.3-35)	5 (1.7)	23.6 (10.2-42.5)	16.7 (9-31.5)	**0.029**
Operation time, min (IQR)		302 (255-375)	48 (16.3)	306 (262.8-358.5)	298.5 (249.8-384.5)	0.821
CPB time, min (IQR)		145 (117.8-172.3)	34 (11.6)	145 (117 – 171.8)	144.5 (119.3 - 172.5)	0.928
Cross-clamp time, min (IQR)		96 (76-120)	37 (12.6)	96.5 (80-118.5)	94 (74-120)	0.39

Abbreviations: POAF, postoperative atrial fibrillation; CABG, coronary artery bypass grafting; IQR, interquartile range; CPB, cardiopulmonary bypass

Table 3. Postoperative outcomes

Postoperative outcomes/findings

	All patients	Missing	POAF+	POAF-	p value
	n = 294	n, (%)	n=127 (%)	n=167 (%)	
Pericardial effusion, mm (IQR)	5.9 (0-12.5)	0	8.5 (0-15.8)	0 (0-9.3)	**< 0.001**
Postoperative anticoagulant	226 (76.9)	0	102 (80.3)	124 (74.3)	0.264
Postoperative antiplatelet	130 (44.2)	0	50 (39.4)	80 (47.9)	0.156
Short term re-operation	14 (4.8)	0	6 (4.7)	8 (4.8)	1
30-day mortality	6 (2.0)	2 (0.7)	5 (3.9)	1 (0.6)	0.088
Stroke	14 (4.8)	2 (0.7)	8 (6.3)	6 (3.6)	0.408
Renal failure	7 (2.4)	2 (0.7)	5 (3.9)	2 (1.2)	0.245
Infection	36 (12.2)	2 (0.7)	18 (14.2)	18 (10.8)	0.377
Hemorrhage or tamponade	8 (2.7)	2 (0.7)	4 (3.1)	3 (1.8)	0.73
Mediastinitis	5 (1.7)	2 (0.7)	0 (0)	5 (3.0)	0.072
Prolonged ventilation >21 days	25 (8.5)	2 (0.7)	11 (8.7)	14 (8.4)	1

Abbreviations: POAF, postoperative atrial fibrillation; IQR, interquartile range

Table 4. Multivariate analysis of previously published POAF risk factors with multiple imputation

Multivariate analysis with multiple imputation

	Odds ratio	95% CI	p value
Age (per 1 year)	1.07	1.04 - 1.10	**< 0.001**
Male (vs. female)	1.16	0.66 - 2.04	0.614
HT	0.70	0.36 - 1.35	0.286
DM	1.29	0.67 - 2.46	0.443
COPD	0.65	0.25 - 1.70	0.377
CKD	1.00	0.52 - 1.92	0.999
CHF	1.23	0.51 - 3.00	0.644
Vascular disease	0.71	0.37 - 1.39	0.32
Stroke or TIA	1.96	0.90 - 4.25	0.087
CABG	1.30	0.64 - 2.65	0.463
Valve surgery	1.09	0.56 - 2.10	0.800
Aortic surgery	0.44	0.22 - 0.88	**0.019**
Intraoperative bleeding (per 1 dL)	1.02	1.00 - 1.03	**0.002**
Postoperative PE (per 1 mm)	1.04	1.01 - 1.08	**0.006**

Abbreviations: HT, hypertension, DM, diabetes mellitus, COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, chronic heart failure; TIA, transient ischemic attack; CABG, coronary artery bypass grafting; PE, pericardial effusion

Figures

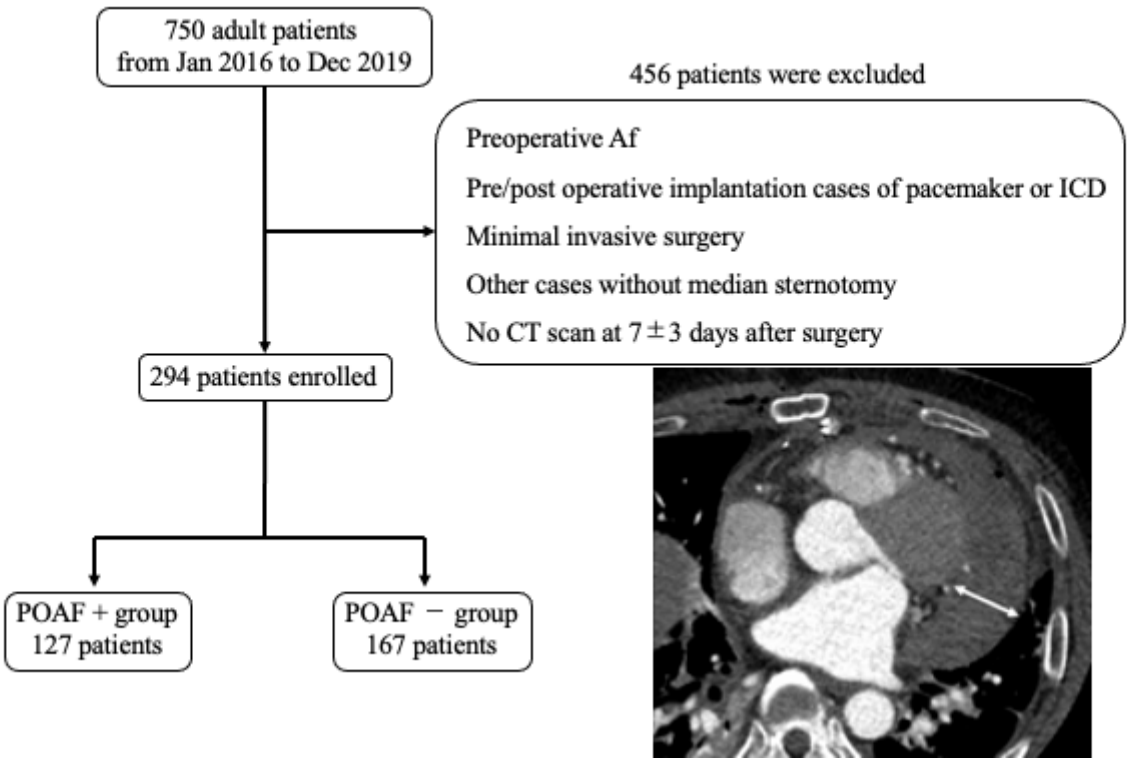

Figure 1

Patient selection flow chart and calculation of pericardial effusion (PE) using computed tomographic images.

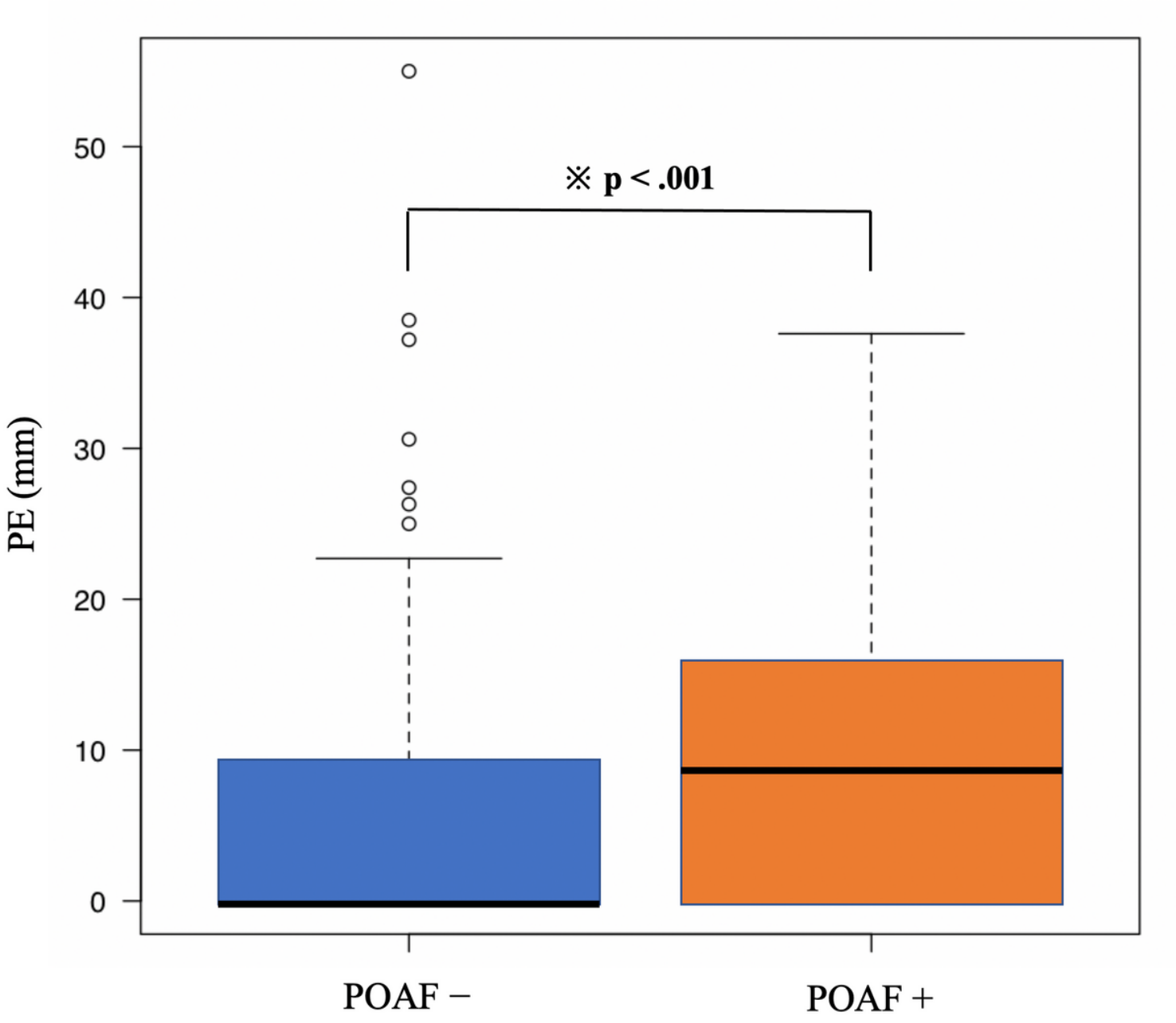

Figure 2

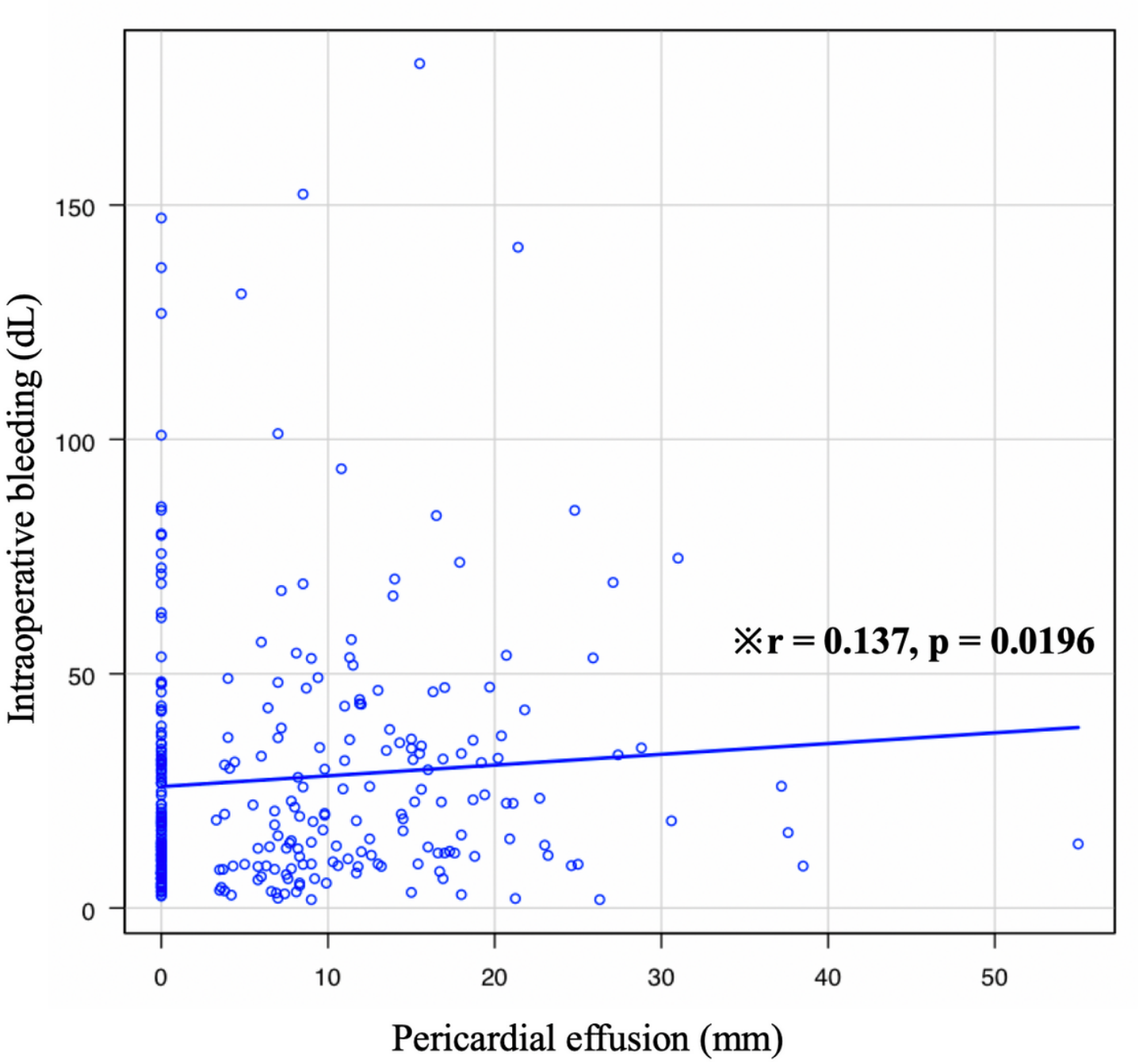

Figure 3

The correlation of intraoperative bleeding volume and pericardial effusion (PE).