Balloon pulmonary angioplasty is effective for treating peripheral-type chronic thromboembolic pulmonary hypertension in elderly patients

Running head: Effect of BPA in elderly CTEPH patients

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Abstract

Aim: Balloon pulmonary angioplasty (BPA) has recently been established as an effective therapy for peripheral-type chronic thromboembolic pulmonary hypertension (CTEPH). However, the safety and effectiveness of BPA in elderly patients with CTEPH have not been clarified.

Methods: Nineteen patients with CTEPH who underwent BPA were recruited. The patients were assigned to groups by age, < 70 years [non-elderly (NE); n = 11)] and ≥ 70 years [elderly (E); n = 8]. Hemodynamic parameters, right ventricular function, and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) were assessed before and after BPA, and complications arising after BPA were also evaluated.

Results: Hemodynamic parameters and right heart function did not differ significantly between the two groups at baseline. BPA significantly improved pulmonary arterial pressure, pulmonary vascular resistance, and fractional area change in both groups (all $P < 0.05$), although the differences were comparable. No fatal complications developed, but the frequency of minor complications such as transient hemoptysis was higher in the E group than in the NE group [median 0.45 (interquartile range 0.27-0.63) vs. 0 (0-0.33), respectively; P=0.021]. The frequency of such complications was also higher in patients with a psychiatric disorder than in those without [0.50 (0.44-1.00) vs.

0.14 (0-0.33), respectively; P=0.006]. Multivariate regression analysis identified higher age, baseline NT-proBNP values, and an underlying psychiatric disorder as significant predictor of complications of BPA.

Conclusion: BPA is an effective treatment for peripheral-type CTEPH regardless of age; however, higher age, NT-proBNP values before treatment, and an underlying psychiatric disorder may be associated with minor complications.

Keywords Balloon pulmonary angioplasty, Chronic thromboembolic pulmonary hypertension, Psychiatric disorder

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a fatal and rare disease, and it is classified into the peripheral-type and central-type by the site of the pulmonary artery obstruction. Although pulmonary endarterectomy (PEA) is an established surgical therapy for CTEPH, PEA is limited to central-type and is not feasible for peripheral-type CTEPH. Furthermore, the PEA procedure is a difficult and invasive therapy that may not be suitable for patients who are elderly or in poor condition. Recently, balloon pulmonary angioplasty (BPA) has been established as an effective therapy for peripheral-type CTEPH and residual pulmonary hypertension after PEA. BPA is an interventional treatment that uses a balloon catheter to dilate thromboembolic pulmonary arteries and is less invasive than PEA. Several reports have demonstrated the efficacy and safety of BPA **[1-6]**. Therefore, BPA could become an alternative therapy for elderly CTEPH patients for whom PEA is not suitable. However, the efficacy and safety of BPA in elderly patients have not been fully investigated. In the present study, the safety, efficacy, and complications of BPA were investigated in elderly and non-elderly patients with CTEPH, and the differences between the two groups were examined.

Methods

Patient population: Nineteen patients with CTEPH, including six patients with a psychiatric disorder, (age, 67.9 ± 9.1 years; male, n = 3) who underwent BPA and follow-up right heart catheterization (RHC) after more than one month from the final BPA between September 2013 and March 2016 were recruited in Nagasaki University Hospital. All patients had been diagnosed with CTEPH by transthoracic echocardiography, lung ventilation-perfusion scintigraphy, contrast-enhanced lung computed tomography, and pulmonary angiography. The patients were assigned to groups by age: < 70 years [non-elderly (NE); n = 11] and ≥ 70 years [elderly (E); n = 8]. The age of the E group was set as ≥ 70 years in the present study given the age distribution of the enrolled patients (age, 67.9 ± 9.1 years; median value, 68 years). Hemodynamic parameters were assessed using RHC, right ventricular function was assessed using echocardiography, and plasma NT-proBNP, 6-min walk distance (6MWD) before and after BPA, and complications arising after BPA were also evaluated. This study complied with the Declaration of Helsinki with regard to investigations in humans, and the Ethics Committee of Nagasaki University Hospital approved the protocol. All patients provided their written, informed consent before RHC.

BPA procedure: Before the BPA procedure, the branches of the pulmonary arteries to dilate were selected based on the findings of contrast-enhanced lung computed tomography, lung ventilation-perfusion scintigraphy, and pulmonary angiography. A 9-Fr short sheath was inserted through the right jugular vein or femoral vein, and a bolus of 2000 U of heparin was injected, followed by repeated injection of heparin (1000 – 2000 U) to maintain the activated clotting time at 200-300 s. After measuring hemodynamics, a 6-Fr guide catheter was inserted through the long sheath located at the main pulmonary artery tract, and a 0.014-inch guide wire crossed the target lesion with or without a micro-catheter. After pulmonary angiography, the characteristics of the target lesions were evaluated by intravascular ultrasound (IVUS) and/or optical coherence tomography (OCT), and then the balloon catheter size was determined. The BPA procedure was finished based on the procedure time or the dose of contrast medium, maximum of 180 minutes or 250 ml, respectively. The BPA session was repeated until the mean pulmonary artery pressure (PAP) reached < 25 mmHg.

Complications related to BPA

Complications of each BPA session were examined. Reperfusion edema was confirmed by chest radiographic opacity in the dilated area by BPA. Vessel injuries were defined angiographically as dissection or contrast media extravasation of pulmonary arteries. The frequency of complications per BPA session was calculated as the number of BPA sessions in which complications occurred divided by the total number of BPA sessions in each patient.

Statistical analysis: All statistical analyses were performed with JMP Pro 11 (SAS Institute Inc., Cary, NC, USA). The distribution of the data for normality were evaluated with the Shapiro-Wilk test, and the results are expressed means ± SD for normally distributed variables and medians (interquartile range) for skewed variables. Categorical data was analyzed by chi-square test. Significant differences between the two groups were determined using the unpaired *t*-test or the Wilcoxon rank-sum test. Differences in frequencies were analyzed using Fisher's exact probability test. Differences between variables at baseline and after BPA were tested by the paired *t*-test or the Wilcoxon signed-rank test. Relationships between parameters [age, mean PAP, pulmonary vascular resistance (PVR), and NT-proBNP] and the frequency of complications per BPA session were evaluated using Spearman's rank correlation coefficient. Significant factors associated with the frequency of complications per BPA session were determined by univariate and multivariate linear regression analyses. $P < 0.05$ was considered significant.

Results

Baseline characteristics

The baseline characteristics of the NE and E groups are shown in Table 1. WHO functional class, hemodynamic parameters [mean PAP, mean right atrial pressure (RAP), cardiac output (CO), PVR], right heart function [tricuspid valve regurgitation pressure gradient (TRPG), right ventricular dimension (RVD), fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE)] and the HASBLED score did not differ significantly between the two groups at baseline.

Changes in hemodynamics, right heart function, NT-proBNP, 6MWD, and WHO functional class by BPA

Although the total number of BPA sessions was not significantly different between the NE and E groups (2.8 ± 1.8 vs. 3.8 ± 1.0, respectively, P = 0.215), the number of branches per BPA session was less in the E group (3.5 ± 0.9) than in the NE group (4.5 ± 0.7, P = 0.013).

BPA significantly reduced mean PAP and PVR, but did not significantly change CO in both groups [NE group 4.4 (3.8-5.4) to 4.4 (4.2-5.0) L/min, P = 0.650; E group 4.0 (3.4-4.7) to 4.2 (3.8-4.6) L/min, P = 0.791]. Echocardiographic parameters, such as TRPG, RVD, and FAC, were also significantly improved by BPA. TAPSE increased after BPA only in the NE group (18.6 ± 2.6 to 22.0 ± 4.2 mm, P = 0.049). NT-proBNP levels were higher in the E group than in the NE group at baseline [400.0 (338.0-956.4) vs. 141.2 (64.6-361.7) pg/ml, P = 0.035], and BPA significantly decreased NT-proBNP levels in both groups. 6MWD was similar at baseline and significantly improved by BPA in both groups (NE group 301.0 ± 95.9 to 337.2 ± 53.7 m, P = 0.011; E group 317.8 ± 80.9 to 390.4 ± 91.0 m, P = 0.011). The WHO functional classification was significantly improved by BPA in both groups. The differences between before and after BPA in the parameters mentioned above did not differ significantly between the two groups (Table 2).

Complications related to BPA

A total of 61 BPA sessions were performed for all patients (31 sessions in the NE group and 30 sessions in the E group) (Table 3). There was no significant difference in the prevalence of vessel injuries in the NE and E groups (12.9% vs. 20.0%, respectively; P = 0.508). Reperfusion lung edema occurred in 4 sessions (1 session in the NE group vs. 3 sessions in the E group, P = 0.354), and non-invasive positive pressure ventilation was needed in 3 sessions in the E group (vs. none in the NE group, P = 0.113). Hemoptysis occurred more often in the E group than in the NE group (40.0% vs. 9.7%, respectively; P = 0.008). One patient with atelectasis caused by hemoptysis was treated by bronchoscopy. The proportion of total complications including transient hemoptysis and angiographic vessel injury for total BPA sessions was significantly higher in the E group than in the NE group (50.0% vs. 16.1%, respectively; P = 0.007). No fatal complications requiring invasive mechanical ventilator and/or percutaneous cardiopulmonary support developed.

The E group had a higher frequency of complications per BPA session than the NE group [0.45 (0.27-0.63) vs. 0 (0-0.33), respectively, P = 0.021]. The frequency was correlated with age (rho = 0.534, p = 0.019), NT-proBNP (rho = 0.600, p = 0.007), mean PAP (rho = 0.545, p = 0.016), and PVR (rho = 0.645, p = 0.003).

The relationships between such complications and the presence of a psychiatric disorder was also examined based on our clinical experience. Patients with a psychiatric disorder, who were diagnosed by psychiatrists or had taken antipsychotic agents, had a higher frequency of complications per BPA session compared to those without a psychiatric disorder [0.50 (0.44-1.00) vs. 0.14 (0-0.33), respectively; P = 0.006]. Lower CO and higher PVR were also observed in patients with a psychiatric disorder (Figure 1). On multivariate linear regression analysis, higher age and baseline NT-proBNP values, as well as an underlying psychiatric disorder, were significant predictors of complications of BPA (Table 4).

Discussion

The present study demonstrated that: (1) BPA improved pulmonary hemodynamics and clinical status in not only non-elderly, but also elderly patients with peripheral-type CTEPH; (2) no major complications associated with BPA occurred in both groups; and (3) higher age and baseline NT-proBNP values, as well as underlying psychiatric disorders, were significant predictors of complications of BPA.

The prognosis of medically treated CTEPH patients with mean PAP >30 mmHg has been reported to be very poor **[7]**. Sugimura et al. reported that inoperable CTEPH had a poor prognosis with historical therapy, and their 5-year survival was about 60% **[1]**. BPA for CTEPH was first reported in 1988 **[8]**, and Feinstein et al. showed the efficacy and safety of BPA in 18 patients with CTEPH, in which 11 patients developed reperfusion pulmonary edema, and 2 patients eventually died, despite improvements of pulmonary hemodynamics and exercise capacity **[9]**. Therefore, BPA has not been widely accepted because of such complications associated with the BPA procedure. Recently, several studies, especially in Japan, demonstrated that BPA was a promising treatment in peripheral-type and inoperable CTEPH patients with fewer complications and a better prognosis **[1-3, 5, 6]**. However, the efficacy and safety of BPA in elderly patients had not yet been clarified.

In the present study, there were significant improvements in pulmonary hemodynamics (mean PAP and PVR), right ventricular function (TRPG, RVD, TAPSE, and FAC), 6MWD, and WHO FC, and NT-proBNP, but not CO, in both groups. The differences in these parameters before and after BPA were not significantly different between the NE and E groups. Additionally, mean PAP after BPA was lower in the present study than in the previous reports (19.3 ± 4.1 mmHg in the present study, 31.8 ± 10.0 mmHg in the report of Kataoka et al., and 24.0 ± 6.4 mmHg in the report of Mizoguchi et al.) **[2, 3]**, suggesting that the procedure achieved a sufficient effect. Yanagisawa et al. demonstrated that BPA improved mean PAP, PVR, BNP, and 6MWD in both the younger group (< 65 years) and the elderly group (≥ 65 years), and the degrees of the improvements in these parameters were comparable between the two groups. There was also a significant improvement in WHO FC in both groups; however, the degree of improvement was significantly different between the two groups because WHO FC was more severe in the elderly group at baseline **[10]**. The results were similar to the present results, although no significant difference between the two groups in the degree of improvement in WHO FC was found in the present study. These findings suggested that BPA was an effective treatment for not only non-elderly, but also elderly patients with peripheral-type CTEPH.

Regarding the safety of BPA in elderly patients, the prevalence of reperfusion pulmonary edema and vessel injuries such as wire perforation and pulmonary artery dissection at each BPA session were comparable between the NE and E groups. This agreed with the results of a previous report **[10]**. However, the frequency of clinical symptoms such as hemosputum and hemoptysis was higher in the E group than in the NE group. Eventually, the frequency of all complications was higher in the E group than in the NE group. Most of the symptoms were promptly treated with a hemostatic agent during the procedure. No serious complications requiring invasive mechanical ventilator and/or percutaneous cardiopulmonary support were found in both groups; therefore, there were no peri-procedural deaths in the present study. These findings suggest that BPA can be performed safely even in elderly patients, but it is necessary to pay attention to the clinical symptoms that develop during the procedure.

In the present study, in addition to high age, the factors associated with complications were baseline NT-proBNP and underlying psychiatric disorders. Kataoka et al. reported that higher baseline BNP levels were the risk factor for reperfusion pulmonary edema **[2]**. Given that NT-proBNP is a biomarker of heart failure and related to the prognosis, the severity of illness is associated with complications related to BPA.

Associations between psychiatric disorders and venous thromboembolism (VTE) have been reported. VTE often develops during the course of schizophrenia and depression **[11].** The unique pharmacological effects of some psychotropic drugs, serotonin-mediated platelet aggregation and pulmonary vasoconstriction, and a decreased activity due to antipsychotic drugs are associated with an increased risk of VTE **[11-14]**. There are some case reports of CTEPH in patients taking psychotic drugs, but there have been no reports of the relationship between BPA complications and psychiatric disorders **[15-17]**. In the present study, patients with psychiatric disorders had lower CO and higher PVR than those without. The sedative effect of psychotic drugs and bed rest cause muscle weakness, as well as dehydration, which may decrease CO and increase PVR. High PVR is considered to be associated with a high risk of complications following BPA. In addition, NT-proBNP levels tended to be higher in patients with psychiatric disorders than in those without [424.1 (272.0-3088.8) vs. 268.4 (96.1-392.6) pg/ml, P = 0.105]. This result suggested that patients with psychiatric disorders had a more severe condition at baseline than those without, which may have increased complications. Furthermore, patients with psychiatric disorders were often non-cooperative with respect to breath-holding and the resting position during the BPA procedure. Breath-holding was particularly important when passing the wire into the target branch. This may also be a cause of the high frequency of complications, such as wire perforation and hemosputum, in these patients.

There are several limitations to this study. This study was a retrospective analysis of a small patient cohort from a single center. In addition, long-term outcomes of BPA-treated patients were not evaluated. A large-scale prospective study is needed. In addition, the majority of patients were female (84.2%) in the present study; this predominance is not considered to be related to any selection bias in this study, because 72.2% of Japanese patients with CTEPH are women **[18]**.

In conclusion, BPA is an effective treatment for peripheral-type CTEPH in not only non-elderly patients, but also elderly patients. However, higher age, NT-proBNP values before treatment, and psychiatric disorders may be associated with minor complications, so we should pay attention to complications when we perform BPA in such patients.

Acknowledgment

There was no grant support for this manuscript.

Disclosure statement

The authors declare no conflict of interest.

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Figure Legend

Figure 1. Comparisons of the frequency of complications per balloon pulmonary angioplasty session (a) and baseline hemodynamics, such as mean pulmonary arterial pressure (PAP) (b), cardiac output (CO) (c), and pulmonary vascular resistance (PVR) (d), between patients with psychiatric disorders (+; n = 6) and those without (-; n = 13). *: significant ($P < 0.05$) difference between patients with psychiatric disorders and those without.

Table 1. Patients' characteristics

Variables	Non-elderly group (n = 11)	Elderly group (n = 8)	P-value
Age, years	61.9 ± 6.5	76.3 ± 3.9	<0.001
Women/men	9/2	7/1	-
WHO FC, n			
I	0	0	
II	2	1	
III	9	7	
IV	0	0	
BMI, kg/m^2	22.5 ± 2.1	22.2 ± 1.5	0.719
Psychiatric disorder, n	2	4	0.319
Right heart catheterization			
Mean PAP, mmHg	38.0 ± 10.3	43.0 ± 6.8	0.246
Mean PAWP, mmHg	7.0 (6.0-7.0)	6.5 (5.0-8.8)	0.866
Mean RAP, mmHg	3.0 (3.0-6.0)	5.0 (2.5-5.8)	0.706
CO, L/min	4.4 (3.8-5.4)	4.0 (3.4-4.7)	0.364
PVR, Wood units	6.7 ± 3.3	8.6 ± 1.7	0.162
Echocardiography			
TRPG, mmHg	59.0 ± 13.8	73.1 ± 23.1	0.113
RVD, mm	35.0 (30.0-40.0)	35.5 (29.0-39.5)	1.000
FAC, %	31.5 ± 12.4	28.4 ± 8.5	0.542
TAPSE, mm	16.8 ± 3.3	18.6 ± 2.6	0.222

NT-proBNP, pg/ml	141.2 (64.6-361.7)	400.0 (338.0-956.4)	0.035
6MWD, m	301.0 ± 95.9	317.8 ± 80.9	0.694
Medicines			
Warfarin, n	9	6	1.000
DOAC, n	2	2	1.000
HASBLED-score	1 (1-2)	2 (1-2)	0.360

Data are expressed as mean ± SD or medians (interquartile 25% and 75%). WHO FC, world health organization functional class; BMI, body mass index; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; CO, cardiac output; PVR, pulmonary vascular resistance; TRPG, tricuspid regurgitation pressure gradient; RVD, right ventricular dimension; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6MWD, 6-min walk distance; DOAC, direct oral anticoagulant.

Table 2. Changes of parameters following BPA

Variable	Non-elderly		P value	Elderly		P value	P value NE vs. E
	Before	After		Before	After		
Mean PAP, mmHg	38.0 ± 10.3	21.3 ± 5.8	<0.001	43.0 ± 6.8	19.8 ± 3.1	<0.001	0.157
PVR, Wood units	6.7 ± 3.3	3.4 ± 1.7	0.005	8.6 ± 1.7	3.5 ± 1.0	<0.001	0.132
CO, L/min	4.4 (3.8-5.4)	4.4 (4.2-5.0)	0.650	4.0 (3.4-4.7)	4.2 (3.8-4.6)	0.791	1.000
TRPG, mmHg	59.0 ± 13.8	35.9 ± 12.3	<0.001	73.1 ± 23.1	36.0 ± 8.0	<0.001	0.080
RVD, mm	35.0 (30.0-40.0)	30.0 (25.0-33.0)	<0.001	35.5 (29.0-39.5)	27.5 (26.3-29.0)	0.016	0.412
FAC, %	31.5 ± 12.4	39.1 ± 10.7	0.025	28.4 ± 8.5	42.5 ± 2.7	<0.001	0.112
TAPSE, mm	16.8 ± 3.3	18.9 ± 3.9	0.097	18.6 ± 2.6	22.0 ± 4.2	0.049	0.495
NT-pro BNP, pg/ml	141.2 (64.6-361.7)	87.8 (44.9-170.9)	0.019	400.0 (338.0-956.4)	159.6 (116.3-231.3)	0.008	0.076
6MWD, m	301.0 ± 95.9	337.2 ± 53.7	0.011	317.8 ± 80.9	390 ± 91.0	0.011	0.361
WHO FC, n	2.8 ± 0.4	1.7 ± 0.45	<0.001	2.9 ± 0.4	1.8 ± 0.5	<0.001	0.954

P value, Differences before vs. after BPA; P value NE vs. E, Differences of changes between non-elderly and elderly patients;
Data are expressed as mean ± SD or medians (interquartile 25% and 75%). PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; CO, cardiac output; TRPG, tricuspid regurgitation pressure gradient; RVD, right ventricular dimension; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6MWD, 6-min walk distance; WHO FC, world health organization functional class.

Table 3. Complications related to BPA

Variables	Non-elderly group	Elderly group	P-value
Total number of BPA sessions, n	2.8 ± 1.8	3.8 ± 1.0	0.215
The number of branches per BPA session, n	4.5 ± 0.7	3.5 ± 0.9	0.013
Death, n (%)	0 (0%)	0 (0%)	-
Intratracheal intubation, n (%)	0 (0%)	0 (0%)	-
Percutaneous cardiopulmonary support, n (%)	0 (0%)	0 (0%)	-
Reperfusion edema, n (%)	1 (3.2%)	3 (10.0%)	0.354
Vessel injuries, n (%)	4 (12.9%)	6 (20.0%)	0.508
Hemosputum or hemoptysis, n (%)	3 (9.7%)	12 (40.0%)	0.008
Total number of complications, n (%)	5 (16.1%)	15 (50.0%)	0.007

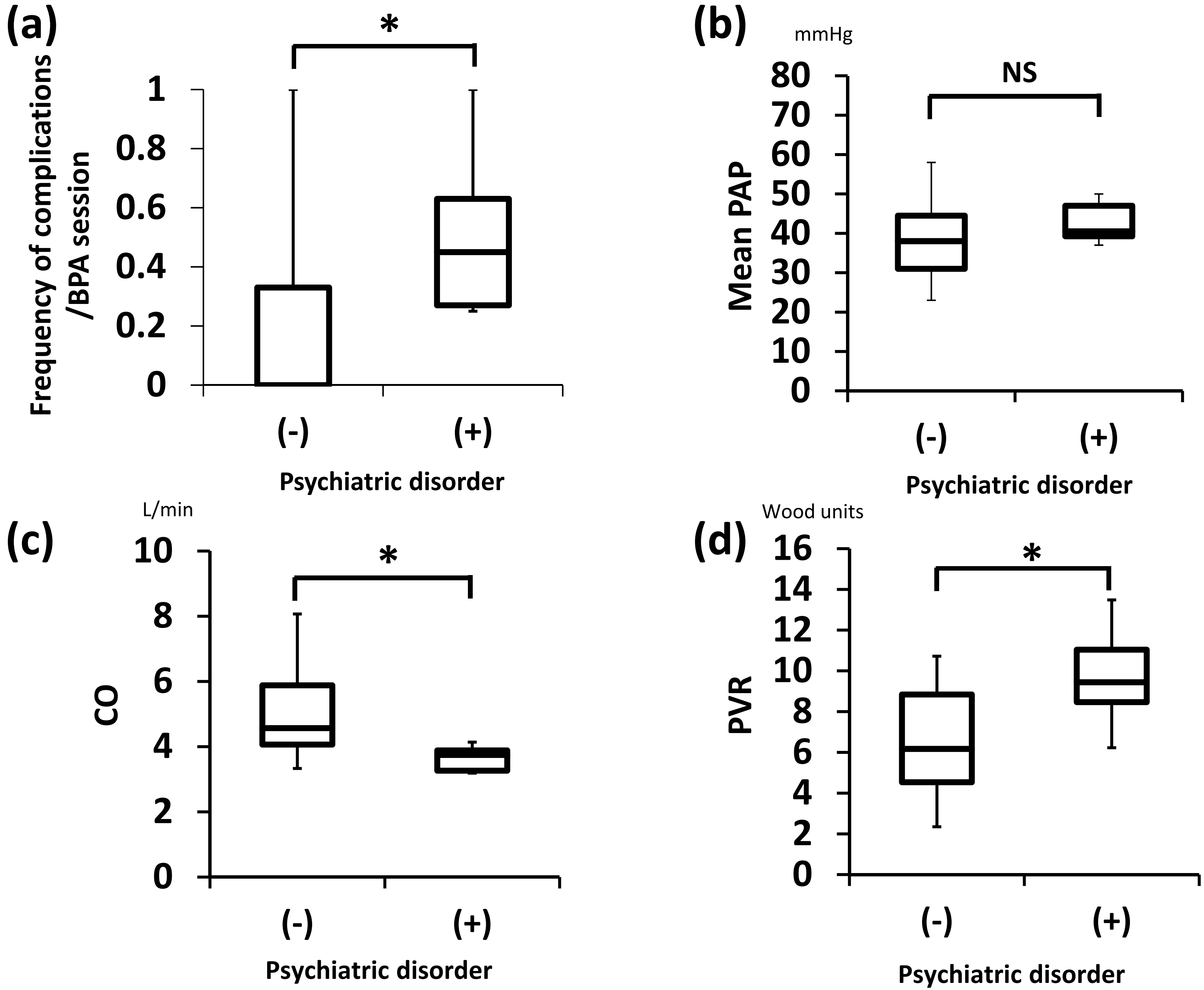
Data are given the number of sessions in each group, with percentages in parentheses.

Table 4. The factors associated with the frequency of complications by BPA

	Univariate analysis		Multivariate analysis	
	coefficient β	P-value	coefficient β	P-value
Age	0.42	0.073	0.33	0.017
Mean PAP	0.50	0.029	0.18	0.356
PVR	0.69	0.001	-0.01	0.960
NT-proBNP	0.73	<0.001	0.52	0.006
Psychiatric disorder	-0.67	0.002	0.34	0.046

PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Figure 1



(a)
*
Frequency of complications /BPA session
1
0.8
0.6
0.4
0.2
0
(-)
(+)
Psychiatric disorder
(b)
mmHg
NS
Mean PAP
80
70
60
50
40
30
20
10
0
(-)
(+)
Psychiatric disorder
(c)
L/min
*
CO
10
8
6
4
2
0
(-)
(+)
Psychiatric disorder
(d)
Wood units
*
PVR
16
14
12
10
8
6
4
2
0
(-)
(+)
Psychiatric disorder