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Original Article

Oxygen inhalation can selectively dilate pulmonary arteries in patients with chronic thromboembolic pulmonary hypertension before balloon angioplasty

Masataka Shigetoshi, MD[a], Kunihiko Hatanaka, MD, PhD[a], Aiko Ogawa, MD, PhD[b], Isao Tabuchi, MD[a], Hiroto Shimokawahara, MD, PhD[a], Mitsuru Munemasa, MD, PhD[a], Hiroshi Ito, MD, PhD[c], Hiromi Matsubara, MD, PhD[a, *]

[a]Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

[b]Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan

[c]Department of Cardiovascular Medicine, Okayama University, Okayama, Japan

*** Corresponding author:**

Hiromi Matsubara, MD, PhD

Department of Cardiology, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama 701–1192, Japan

E-mail: matsubara.hiromi@gmail.com

Tel: +81-86-294-9911

Fax: +81-86-294-9255

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Abstract

Background: Pulmonary injury is a major complication of balloon pulmonary angioplasty (BPA) for chronic thromboembolic pulmonary hypertension (CTEPH). Lung injury after BPA can be exacerbated by a high mean pulmonary arterial pressure (PAP). Although oxygen inhalation is expected to lower mean PAP in patients with CTEPH, no relevant investigation has been conducted.

Methods: Consecutive patients with CTEPH who underwent BPA were enrolled in this study. We evaluated the hemodynamics using right heart catheterization while breathing ambient air and with administration of 5 L/min oxygen for 10 min.

Results: This study included 52 consecutive patients with CTEPH, of which 23 (44%) were treated with specific pulmonary vasodilators. Exposure to oxygen was well tolerated. Oxygen administration significantly decreased mean PAP by 3.8 ± 3.2 mmHg ($p<0.001$) and pulmonary vascular resistance by 0.8 ± 1.8 Wood units ($p<0.001$). Moreover, the ratio of pulmonary vascular resistance to systemic vascular resistance was significantly reduced by 13.5% ($p<0.001$). Multivariate regression analysis identified baseline mean PAP ($\beta=0.395$, $p=0.045$) as the only

significant predictor of decreased mean PAP under oxygen administration. No significant difference in oxygen effect on mean PAP was found between patients with and without vasodilators.

Conclusions: In patients with CTEPH, 5 L/min supplemental oxygen inhalation could decrease mean PAP significantly by selective pulmonary artery dilatation, regardless of the usage of vasodilators, and thus could be helpful to maximize the safety of BPA.

Clinical Trial Registration: UMIN Clinical Trials Registry (No.: UMIN000026882); URL: http://www.umin.ac.jp/ctr/index.htm.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, progressive pulmonary vascular disease which usually begins with persistent obstruction of a large and/or middle-sized pulmonary artery following acute pulmonary embolism, and microangiopathy could contribute to the progression of the disease [1]. Patients with CTEPH have poor prognosis if untreated [2], and the only established and potentially curative treatment is pulmonary endarterectomy, which is considered the gold standard therapy.

Balloon pulmonary angioplasty (BPA) is an alternative treatment for inoperable CTEPH, which uses balloon catheters for dilatation of pulmonary artery stenosis. In 2001, Feinstein et al. reported the efficacy of BPA in a series of patients with CTEPH [3]; however, the procedure was not widely adopted because of the high incidence of lung injury, which is a potentially lethal complication. Recently, some institutions, including ours, refined BPA to overcome the low efficacy and high complication rates [4,5]. Although BPA is now performed worldwide and has been described as a therapeutic option in the latest guideline [6], the refined BPA procedure has not fully overcome the

risk of onset of lung injury. We previously reported that the severity of lung injury after BPA could be exacerbated by a high mean pulmonary arterial pressure (PAP) [7]. Thus, decreasing PAP before BPA may be effective in minimizing the occurrence of clinically apparent lung injury.

Most patients with CTEPH are hypoxemic because of a reduction in ventilation efficiency, which is mainly due to ventilation/perfusion mismatch [8]. Hypoxic pulmonary vasoconstriction is a fundamental physiological mechanism that redirects blood from poorly to better-aerated areas of the lungs to optimize ventilation/perfusion matching [9]. If this phenomenon is relieved with oxygenation, PAP would be decreased, thereby contributing to the safety of BPA by preventing BPA-related lung injury through a safe, inexpensive, and easily accessible approach, i.e., oxygen administration. With this concept, we have routinely administered oxygen as one of the strategies for the safety of BPA procedure.

In 2001, Roberts et al. reported that in patients with pulmonary hypertension, oxygen therapy decreases mean PAP and increases cardiac index (CI) [10]. However, their study mainly included subjects with pulmonary

arterial hypertension, and no patient with CTEPH was involved. Although it was reported that CTEPH and pulmonary arterial hypertension share acute vasoreactivity properties [11], actual data on the acute effects of oxygen administration on patients with CTEPH are scant. Hence, in this study, we aimed to determine how oxygen affects hemodynamics in patients with CTEPH before BPA.

Methods

Consecutive patients with CTEPH who underwent BPA between May 2015 and May 2017 at the National Hospital Organization Okayama Medical Center were enrolled in this study. This study was conducted in accordance with the amended Declaration of Helsinki. This study was approved by the Institutional Review Board of the National Hospital Organization Okayama Medical Center (H26-RINKEN-55), and written informed consent was obtained from each patient. Right heart catheterization was performed while breathing ambient air as a routine assessment of hemodynamics, after which oxygen was administered and hemodynamics were assessed again. After that, first session

of BPA was performed on another day.

The diagnosis of CTEPH was based on detailed medical history, physical examination, chest radiography, chest computed tomography, transthoracic echocardiography, lung ventilation/perfusion scintigraphy, right heart catheterization, and angiographic demonstration of multiple stenosis and obstructions of the bilateral pulmonary arteries [6]. Patients aged ≥20 years were eligible for this study. Exclusion criteria included ischemic heart disease, severe systemic hypertension (≥180/110 mmHg), hypotension (≤85 mmHg), pregnancy, severe valvular heart disease, history of acute myocardial infarction and/or cerebral vascular disease within 6 months, severe ventricular arrhythmia, severe renal dysfunction (serum creatinine ≥2 mg/dL), severe liver dysfunction, chronic inflammatory disease, malignancy, and severely altered hemodynamics and/or respiratory condition contraindicated for oxygen administration.

A thermodilution catheter was inserted into the pulmonary artery through the right internal jugular vein or right femoral vein. Right atrial pressure, mean PAP, pulmonary capillary wedge pressure, and mixed venous oxygen saturation were measured, and cardiac output and CI were determined

by the thermodilution method at baseline, with the patient breathing ambient air. Subsequently, 5 L/min oxygen, which is our routine dose during BPA procedure, was administered by face mask for at least 10 min, and hemodynamics measurements were repeated. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated based on measured hemodynamic parameters. PVR/SVR ratio was also calculated as an indicator of pulmonary selectivity of the vasodilatory effect.

Descriptive data are expressed as mean ± SD or as medians with interquartile ranges for continuous variables and as percentages for categorical variables. Continuous variables before and after oxygen administration were compared using a paired *t* test or Wilcoxon signed-rank test based on data distribution. Univariate analysis based on standard linear regression analysis was used to examine the relationship between the change in mean PAP and the baseline data. Multivariate analysis based on the linear regression analysis was employed to examine the influence of each variable on the improvement of mean PAP; variables were selected based on the results of the univariate analysis and clinical significance. Moreover, variables were compared between patients with

and without vasodilators using Student's unpaired *t* test or Mann-Whitney *U* test based on data distribution, and the interaction between the effects of oxygen and vasodilators was analyzed by two-way repeated-measures analysis of variance. All analyses were performed with IBM SPSS 25 (IBM, Armonk, NY). Statistical significance was defined as $p<0.05$.

Results

Clinical characteristics of the patients are shown in Table 1. Fifty-two patients (mean age 65.2 ± 11.3 years, 41 women [79%]) met the study inclusion criteria. Disease duration, i.e., from symptom onset to study enrollment, was approximately 1.5 years. Twenty-five patients (48%) were in WHO functional class III/IV, and 23 patients (44%) were treated with one or more specific pulmonary vasodilators: riociguat (median 6 mg/day, range 1.5-7.5 mg/day) was administered to approximately one-third of the subjects.

Exposure to oxygen was well tolerated by patients without any discomfort or adverse events. Changes in hemodynamic values before and after oxygen administration are shown in Table 2. Oxygen administration

significantly decreased mean PAP by 3.8 ± 3.2 mmHg ($p<0.001$) or 9.2% from the baseline value (Figure 1). Consequently, PVR significantly decreased by 0.8 ± 1.8 Wood units ($p<0.001$), although CI slightly decreased. The number of patients with mean PAP ≥40 mmHg decreased from 26 (50%) to 18 (35%). Oxygen administration slightly increased SVR, and PVR/SVR was significantly reduced by 13.5% ($p<0.001$).

Univariate linear regression analysis revealed that baseline mean PAP (ß=-0.382, p=0.005) and baseline PVR (ß=0.070, p=0.032) were significantly correlated with the decrease in mean PAP under oxygen administration (Table 3). In the multivariate analysis, only baseline mean PAP (ß=0.395, p=0.045) remained a significant predictor of decreased mean PAP under oxygen administration (Figure 2). Although, given the small coefficient of determination, it is unclear whether oxygen inhalation is less effective in patients with low baseline PAP.

Twenty-three patients received at least one vasodilator, and 29 patients did not receive any pulmonary vasodilators. At baseline, age and hemodynamic data were comparable between groups, except for significantly lower blood

pressure and SVR in patients with vasodilators (Table 4). Although mean PAP was significantly decreased after oxygen administration in both groups, no difference in oxygen effect on mean PAP between patients with and without vasodilators was found (Figure 3).

Discussion

To our knowledge, this is the first study to clarify the acute effect of oxygen administration on patients with CTEPH. This study showed that oxygen inhalation decreased mean PAP by 3.8 mmHg.

Although various studies have shown improvements in subjective symptoms, hemodynamics, and life prognosis after BPA among patients with CTEPH [3–5], we believe that there is still room for the prevention of complications during the procedure. BPA-related lung injury reportedly occurs in 9.6–60% of patients [3,5,12]. Additionally, we previously demonstrated that the requirement for mechanical ventilation was significantly higher in patients with mean PAP ≥40 mmHg [7]. Thus, it is vital to lower mean PAP before BPA. We performed epoprostenol administration preoperatively, which decreased

mean PAP only by 3 mmHg [4]. In a phase III trial of riociguat for patients with CTEPH (CHEST-1), mean PAP decreased by 4.7 mmHg (77% of patients received the maximal dose) [13]. Although riociguat is less expensive than epoprostenol, its effects must be carefully evaluated. In the study protocol, 8 weeks is needed before the dosage of riociguat could be gradually increased up to treatment dose. Furthermore, adverse effects, such as headache, dizziness, and hypotension, were observed, which in turn could limit the dose of the drug. Moreover, a MERIT-1 trial showed a significant decrease in PVR with macitentan, but not in mean PAP, in patients with CTEPH [14].

There has been much interest in the effect of oxygenation on hemodynamics, and PAP reduction by oxygen administration may contribute to the safety of the BPA procedure without additional cost or risk. Previous studies reported that oxygen administration in patients with pulmonary hypertension dilates pulmonary arteries, thereby decreasing the mean PAP. However, the subjects mainly consisted of patients with pulmonary arterial hypertension [10,15,16]. Thus, data on the hemodynamic effect of oxygenation in patients with CTEPH are scarce.

In this study, we showed that mean PAP decreased by 3.8 mmHg with oxygenation, which exceeded the effect of continuous infusion of epoprostenol [4]. The effect was greater in patients with higher mean PAP; consequently, the number of subjects with mean PAP <40 mmHg increased from 26 (50%) to 34 (65%). This improvement in hemodynamics could be explained by two mechanisms: sympathetic tone reduction and release of hypoxic pulmonary vasoconstriction. In this study's subjects, the sympathetic nerve was likely activated, which was indicated by the SVR elevation at baseline. Thus, a decline in heart rate and CI might be the effect of normalization of sympathetic nerve activity following the improvement of hypoxia [17]. In addition, after oxygen inhalation, the magnitude of reduction in PVR was greater than that in SVR. Moreover, the improvement of hypoxic vasoconstriction, which is considered a unique feature of the pulmonary artery [10,18], possibly resulted in selective dilatation of the pulmonary artery. Although it is not clear why SpO_2 at baseline did not correlate with the change in PAP, which is consistent with the finding of a previous study in patients with pulmonary hypertension [15], even in patients with preserved systemic oxygenation, alveolar hypoxia is likely present, which

results in hypoxic vasoconstriction to some extent. In addition, sympathetic activity may account for the correlation between absolute change in mean PAP and baseline mean PAP. Thus, if disease severity in CTEPH is associated with increased sympathetic tone, as reported in pulmonary arterial hypertension [19], reduction in sympathetic activity might have a considerable effect on hemodynamics.

In our study, 44% of the patients were treated with vasodilators, mainly riociguat. However, the beneficial effect of oxygen inhalation on mean PAP was obtained with or without vasodilator use. Currently, although BPA in experienced centers could normalize the hemodynamics in a number of patients with CTEPH who are ineligible for pulmonary endarterectomy [20], some patients are treated with riociguat before BPA, and sequential treatment with riociguat and BPA has been proposed [21]. Nonetheless, oxygen administration is expected to contribute to the safety of BPA regardless of the presence or absence of vasodilator use.

This study has several limitations. This study was conducted at a single center without a control group. Additionally, although we performed right heart

catheterization at baseline after sufficient rest, it is impossible to exclude the effect of additional resting during oxygen inhalation on sympathetic activity. Therefore, resting >10 min during oxygenation possibly affected the hemodynamics by decreasing the sympathetic drive. In addition, the number of patients was extremely limited; thus, the relationship between baseline characteristics, hemodynamics, oximetry parameters, and hemodynamic change could not be fully elucidated. Further investigation by a multicenter study is needed to evaluate the effect of oxygen administration and elucidate the relationship between baseline parameters and hemodynamic change.

It is also desirable to evaluate the effect of reducing BPA complications by oxygen administration. However, it has been performed under oxygen administration from the beginning of BPA in our hospital, and there is no data of BPA without oxygen administration. Moreover, since performing BPA under oxygen administration is recently the standard in many institutions, it is ethically difficult to perform prospective intervention studies at present.

In conclusion, in patients with CTEPH, supplemental oxygen administration (5 L/min) before BPA could remarkably decrease mean PAP by

selective pulmonary artery dilatation. Thus, administering oxygen before BPA would be beneficial, as the safety of the procedure is maximized.

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Figure Legends

Figure 1. The effect of oxygen administration on mean pulmonary arterial pressure (PAP).

Mean PAP significantly improved after oxygen administration by face mask for at least 10 min (n = 52). P<0.01 vs. baseline.

Figure 2. Correlations between the absolute change in mean pulmonary arterial pressure (PAP) and baseline data.

The change in mean PAP was weakly correlated with the mean PAP at baseline (p<0.01).

Figure 3. Mean pulmonary arterial pressure (PAP) at baseline and during oxygen administration in patients with and without vasodilators.

Mean PAP was significantly decreased after oxygen administration in patients with (n=23) and without (n=29) vasodilators. *P<0.05 vs. baseline. No significant interaction for the change of mean PAP between two groups was found (P = 0.383,

analyzed by two-way repeated-measures analysis of variance).

Table 1. Characteristics of the patients at study enrollment

Characteristics	Enrolled patients (n = 52)
Age, years	65.2 ± 11.3
Female, n (%)	41 (79)
Disease duration, days	497 (159–1085)
Exercise capacity	
WHO-FC (II/III/IV), n	27/23/2
6MWD, m	306.0 ± 129.8
BNP, pg/dL	52.5 (17.9–125.4)
Respiratory function test, %	
%VC	92.9 ± 17.8
FEV1%	74.0 ± 7.4
$\%DL_{CO}$	67.3 ± 14.1
$\%DL_{CO}/VA$	71.4 ± 16.5
Home oxygen therapy, n (%)	33 (63)

Medications, n (%)	
Riociguat	19 (37)
ERA	1 (2)
PDE5 inhibitor	1 (2)
Oral prostanoid	8 (15)

Values are expressed as mean ± SD or median (interquartile range) for continuous variables and as percentages for categorical variables.

WHO-FC, WHO functional class; 6MWD, 6-min walk distance; BNP, B-type natriuretic peptide; VC, vital capacity; FEV1, forced expiratory volume in 1 s; DL_{co}, carbon monoxide lung diffusion; VA, alveolar volume;

ERA, endothelin receptor antagonist; PDE5, phosphodiesterase type 5.

Table 2. Baseline hemodynamics and the effect of oxygen administration

	Baseline	Oxygen	p value
HR, beats/min	70.4 ± 13.0	66.4 ± 15.2	<0.001
Mean BP, mmHg	88.0 ± 18.7	87.4 ± 17.3	0.71
SpO_2, %	90.0 (84.5–92.5)	100.0 (99.0–100.0)	<0.001
SvO_2, %	60.0 ± 8.0	71.6 ± 7.5	<0.001
Mean PAP, mmHg	40.4 ± 8.8	36.6 ± 8.1	<0.001
CI, L/min/m^2	2.51 (2.17–2.99)	2.37 (2.09–2.71)	<0.001
PVR, WU	8.5 ± 3.7	7.8 ± 3.2	0.004
SVR, WU	20.5 ± 7.4	22.6 ± 7.8	0.013
PVR/SVR	0.422 ± 0.156	0.365 ± 0.125	<0.001

Results are expressed as mean ± SD or median (interquartile range).

HR, heart rate; BP, blood pressure; SpO_2, oximetric measurements of arterial oxygen saturation; SvO_2, central venous oxygen saturation; PAP, pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; WU, Wood unit

Table 3. Regression analysis of the relationships between absolute change in mean PAP and baseline characteristics or hemodynamics

	Univariate analysis			Multivariate analysis	
	Adjusted r^2	ß	p value	ß	p value
HR, beats/min	-0.016	-0.595	0.675		
Age, years	0.004	-0.152	0.282	-0.147	0.307
Female	-0.01	-0.099	0.485		
Disease duration, days	-0.019	0.024	0.866		
WHO-FC III or IV	-0.015	0.067	0.639		
6MWD, m	0.003	-0.15	0.287		
BNP, pg/dL	-0.02	-0.02	0.887		
Mean BP, mmHg	-0.017	0.057	0.688		
SvO_2, %	-0.008	0.109	0.444		
SpO_2, %	-0.017	0.054	0.706	-0.165	0.303
Mean PAP, mmHg	0.129	-0.382	0.005	-0.427	0.006
CI, L/min/m^2	-0.013	0.085	0.547	-0.021	0.881
PVR, WU	0.07	-0.297	0.032		

SVR, WU	0.009	-0.167	0.236
PVR/SVR	0.017	-0.191	0.175

HR, heart rate; WHO-FC, WHO functional class; 6MWD, 6-min walk distance; BNP, B-type natriuretic peptide; BP, blood pressure; SvO_2, central venous oxygen saturation; SpO_2, oximetric measurements of arterial oxygen saturation; PAP, pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; WU, Wood units.

Table 4. Baseline characteristics and hemodynamics in patients with and without vasodilators

	Vasodilator (-) (n = 29)	Vasodilator (+) (n = 23)	p value
Age, years	62.9 ± 11.7	68 ± 10.5	0.1
HR, beats/min	69.7 ± 12.1	71.4 ± 14.4	0.65
Mean BP, mmHg	95.8 ± 16.7	78.2 ± 16.4	<0.001
SvO_2, %	60.4 ± 8.3	59.6 ± 7.7	0.73
Mean PAP, mmHg	40.5 ± 9.5	40.3 ± 7.9	0.94
CI, L/min/m^2	2.5 ± 0.72	2.74 ± 0.54	0.08
PVR, WU	9.0 ± 4.2	7.8 ± 2.4	0.29
SVR, WU	22.7 ± 8.1	17.7 ± 5.3	0.014
PVR/SVR	0.39 ± 0.16	0.47 ± 0.14	0.059

Values are expressed as mean ± SD.

HR, heart rate; BP, blood pressure; SvO_2, central venous oxygen saturation; PAP, pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular

resistance; SVR, systemic vascular resistance; WU, Wood units

Figure 1.

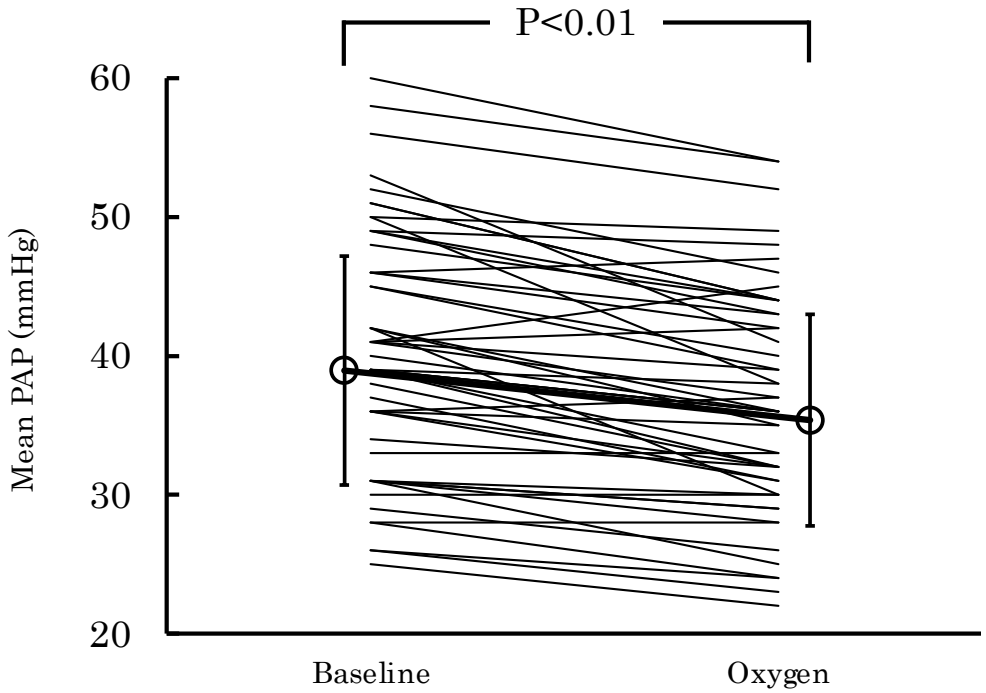
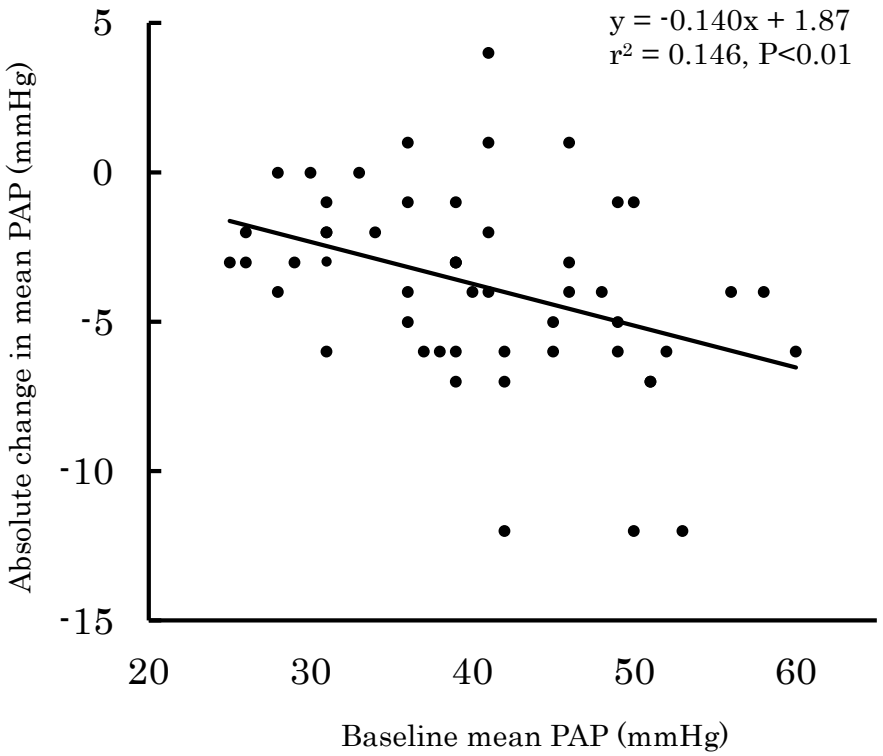


Figure 2.


y = -0.140x + 1.87
r² = 0.146, P<0.01
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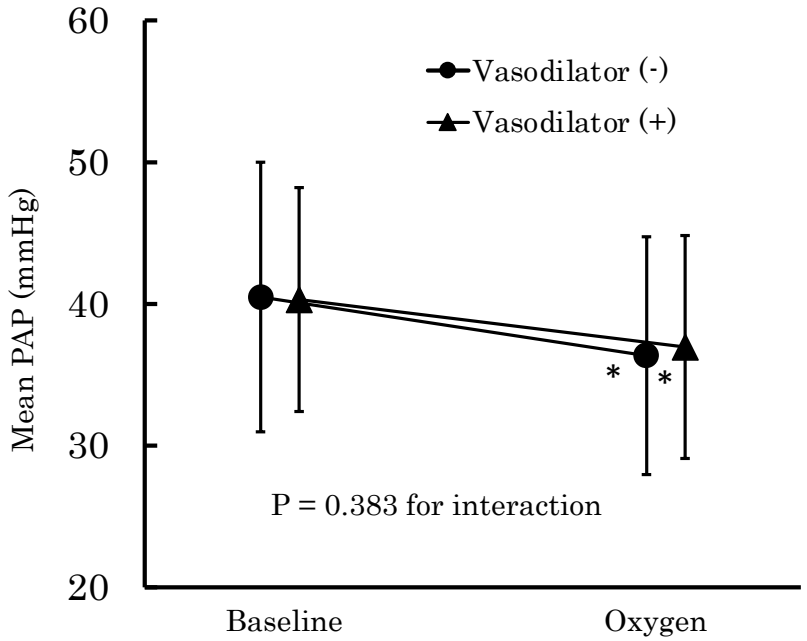
Absolute change in mean PAP (mmHg)
Baseline mean PAP (mmHg)

Figure 3.


60
50
40
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20
Mean PAP (mmHg)
Vasodilator (-)
Vasodilator (+)
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P = 0.383 for interaction
Baseline
Oxygen