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Borderline pulmonary hypertension associated with chronic hypercapnia in chronic pulmonary disease

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ABSTRACT

Pulmonary hypertension (PH) due to lung diseases is classified as group 3 by the Dana Point classification. Given the basic pathophysiological conditions of group 3 lung diseases and the previously well-known concept of hypercapnic pulmonary vasoconstriction, chronic hypercapnia besides alveolar hypoxia might be another causative factor to increase mean pulmonary arterial pressure (PAm). Two hundred twenty-five subjects with chronic pulmonary diseases were assessed by a right heart catheterization and blood gas parameters. The subjects were classified into the following 4 groups: Hypercapnic Hypoxia (HCHX), Hypercapnic Normoxia (HCnx), Normocapnic Hypoxia (ncHX), and Normocapnic Normoxia (ncnx). Compared with ncnx, the HCHX, HCnx and ncHX groups all showed significantly higher PAm and met the criteria of borderline PH. Multiple regression analysis showed that $PaCO_2$, as well as SaO_2, was an independent variable for PAm. Given the poor prognosis with borderline PH, the elimination of excess pulmonary carbon dioxide in hypercapnia could be a considerable treatment strategy in chronic pulmonary disease.

1. Introduction

Pulmonary hypertension (PH) associated with chronic pulmonary disease is classified as group 3 pulmonary hypertension due to lung diseases and/or hypoxia by the world wide PH guidelines (Simonneau et al., 2009; Galiè et al., 2015). Group 3 PH includes chronic obstructive pulmonary disease (COPD), interstitial pneumonitis, pulmonary diseases with mixed restrictive and obstructive pattern, alveolar hypoventilation and sleep breathing disorder.

At the First World Symposium on PH (WSPH) which took place in 1973 at Geneva, Switzerland, the consensus was to define PH as an elevation of mean pulmonary arterial pressure (PAm) greater than or equal to 25 mmHg at rest as assessed by a right heart catheterization (RHC). However, the 6th WSPH which took place recently proposed the new definition of clinical PH as an elevation of mean PAm greater than or equal to 20, given the poor prognosis associated to those with PAm lower than 25 mmHg (Kimura et al., 2012; Heresi et al., 2013; Douschan et al., 2018). This change in definition strongly suggests the pathologic importance of the previously known term, borderline pulmonary hypertension.

The main mechanisms of secondary PH caused by chronic pulmonary diseases are chronic alveolar hypoxia induced pulmonary vasoconstriction (HPV) with subsequent vascular remodeling, a reduction of the pulmonary vascular bed, the effects of abnormal pulmonary mechanics (pleural and alveolar pressure) and inflammation-induced vascular remodeling related to smoking. However, alveolar hypoxia as the most significant mechanism does not necessarily always have an important role in PH since the improvement of PH is not obvious under long-term oxygenation therapy (LTOT) for the COPD (Weitzenblum et al., 1981). Subjects belonging to group 3 have characteristics that are different from patients in other groups. One of these characteristics is that the patients in the group present not only hypoxemia but hypercapnia induced by alveolar hypoventilation and/or ventilation-perfusion (V/Q) mismatch. Even sleep breathing disorder in group 3 present nocturnal episodic hypercapnic hypoxia (Chin et al., 1997) which was confirmed to increase daytime pulmonary arterial pressure in

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human (Chaouat et al., 1996) and in animal (McGuire and Bradford, 2001). Interestingly daytime $PaCO_2$ accounted for 32% of the variance of PAm (Chaouat et al., 1996). Needless to say, sleep breathing disorder is not accompanied with either abnormal pulmonary parenchyma or smoking induced inflammation. Taking into account the previously well-established concept of the vasoconstrictor effect of hypercapnia called the hypercapnic pulmonary vasoconstriction (HCPV) in the seminal paper (von Euler and Liljestrand, 1946) which was highly cited and recently still is (Swenson, 2018; Dorrington et al., 2018), then chronic hypercapnia must also be a key factor that increases pulmonary arterial pressure which leads to PH in chronic pulmonary diseases. Studies focusing on the effects of chronic hypercapnia on pulmonary circulation in patients with chronic pulmonary diseases have not been performed. Therefore, we are the first to evaluate the pulmonary hemodynamics associated with simultaneously obtained blood gas analyses in chronic pulmonary diseases.

2. Materials and methods

2.1. Subjects

We conducted a retrospective chart review of all subjects who underwent a RHC using a balloon-tipped catheter in our department from July 1985 to November 2002. The RHC was usually performed for the purpose of evaluating for any chronic pulmonary diseases, determining its LTOT adaptability, confirming preoperative preparation and evaluation were performed as well as other prep. All subjects provided written informed consent to this procedure according to our institutional guidelines. Subjects with the following characteristics were excluded from our study; (i) those already treated by LTOT, (ii) those with an original diagnosis of PH listed on the guideline except for group 3, and (iii) those with missing data.

2.2. Procedures

2.2.1. Right heart catheterization (RHC)

Swan-Ganz catheter was inserted from the femoral vein or the right internal jugular vein. We measured mean pulmonary arterial pressure (PAm, mmHg), pulmonary artery wedge pressure (PAWP, mmHg) and cardiac output (CO, l/mim) by thermodilution (average of three plausible measurements). We also calculated cardiac index (CI = CO/body surface area, l/min/m^2), pulmonary artery resistance (PAR = [PAm - PAWP]/CO × 1332, dyne·s·cm^{-5}) and total pulmonary vascular resistance (TPR = PAm/CO × 1332, dyne·sec·cm^{-5}).

2.2.2. Pulmonary function procedure

Spirometry was conducted according to the American Thoracic Society recommendations (American Thoracic Society, 1995) and a standard technique using computerized pneumotachograph based equipment (Minato Medical Science, Osaka, JAPAN). Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1) were expressed as a percentage of the predicted value. The ratio of FEV1 divided by FVC (FEV1/FVC) was expressed by as a percentage. The reference values obtained from the Japanese population were utilized to calculate the %predicted values (Japanese Society of Chest Diseases, 1993). Chronic obstructive pulmonary disease (COPD) was defined in patients who exhibited FEV 1 /forced vital capacity (FVC) < 70% and had a smoking history > 10 pack-years. COPD severity was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: GOLD1, mild (FEV 1 ≧ 80% predicted); GOLD2, moderate (50% ≦ FEV 1 < 80% predicted); and GOLD3, severe (30% ≦ FEV 1 < 50% predicted). There were no patients with FEV 1 < 30% predicted.

2.3. Data analysis

We classified the remaining subjects into 4 groups, listed below, according to the presence or absence of hypercapnia from their arterial blood gas analysis ($PaCO_2$≧45 mmHg) and according to the presence or absence of hypoxemia ($PpaO_2$ < 60 mmHg).

1) Hypercapnic Hypoxia (HCHX) ($PaCO_2$≧45 mmHg and PaO_2 < 60 mmHg)
2) Hypercapnic Normoxia (HCnx) ($PaCO_2$ ≧45 mmHg and PaO_2 ≧ 60 mmHg)
3) Normocapnic Hypoxia (ncHX) ($PaCO_2$ < 45 mmHg and PaO_2 < 60 mmHg)
4) Normocapnic Normoxia (ncnx) ($PaCO_2$ < 45 mmHg and PaO_2 ≧ 60 mmHg)

We evaluated the relationships between all the RHC parameters, arterial and venous blood gas parameters and pulmonary function test amongst the 4 groups in chronic pulmonary diseases. We then performed multiple regression analysis to find the independent variables affecting PAm. Present study was approved by the Institutional Review Board at Juntendo University (Approval No. 16-208).

2.4. Statistics

One-way analysis of variance (one-way ANOVA) and a Kruskal-Wallis test with subsequent post hoc test were used to compare between the four groups. Spearman's rank correlation coefficient was used for the correlations of PAm and PAR with the other blood gas parameters. The multiple regression analysis was used to identify the independent factor for PAm. Stepwise regression using backward elimination was employed. Model fit was assessed with the use of the mean squared error, the coefficient of determination (R^2), and an adjusted coefficient of determination (adjusted R^2). It was assumed that there were collinearity characteristics and thus the Variance Inflation Factor (VIF) was applied to detect these where a VIF of 10 or above would indicate a high correlation and a cause for concern. The statistical analysis was carried out using JMP 7.0.2 software (SAS research institute company, Carey, American NC state). All values are expressed as mean ± SD unless otherwise specified. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

Among subjects who were performed RHC, 81 subjects were excluded and 225 subjects were finally included for data analysis (Fig. 1). Table 1 shows the comparison of

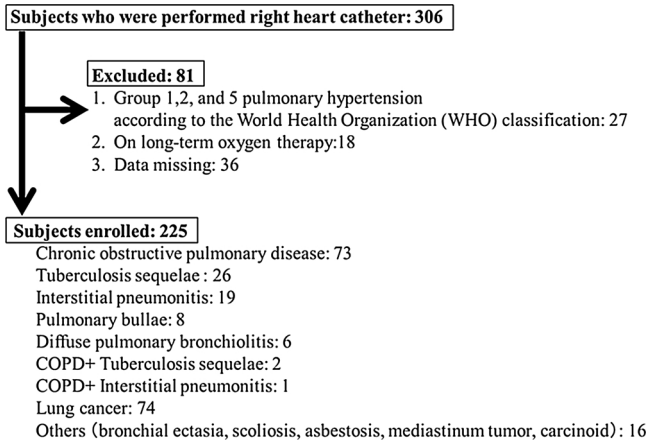

Fig. 1. Flow chart of study cohort formation.

Table 1
Comparison of baseline demographic and characteristics of subjects.

	HCHX	HCnx	ncHX	ncnx
n	11 (male 7/female 4)	19 (male 15/female 4)	8 (male 8/female 0)	187 (male 155/female 32)
Disease	COPD 6, TBsq 4, Scoliosis 1	COPD 4, TBsq 11, DPB 2, BE 1, Asbestosis 1	COPD 2, IP 1, DPB 3, COPD + IP 1, COPD + TBaq 1	COPD 62, IP 18, TBsq 11, Giant bulla 8, Lung cancer 74, COPD + IP 1, Others 13
COPD GOLD	GOLD 3 4, GOLD4 2	GOLD 3 1, GOLD4 3	GOLD 3 2	GOLD1 11, GOLD2 31, GOLD3 12, GOLD4 8
Age	60.5 ± 10.3 (39.0 -72.0)	59.7 ± 9.3 (41.0 -72.0)	62.6 ± 9.5 (45.0 -74.0)	56.7 ± 11.6 (18.0 -77.0)
BMI	18.6 ± 4.8 (14.2 -27.8)	18.2 ± 2.8 (14.0 -26.0)	19.9 ± 3.1 (16.6 -26.2)	21.7 ± 3.1 (14.8-32.0)
pH	7.37 ± 0.02†‡(7.34 -7.41)	7.37 ± 0.03†§(7.30 -7.43)	7.42 ± 0.02 (7.38 -7.45)	7.41 ± 0.03 (7.31 -7.57)
$PaCO_2$, mmHg	52.7 ± 3.8†§(45.8 -57.9)	54.1 ± 8.5†§(45.8 -72.1)	42.4 ± 2.3 (38.1 -44.9)	38.5 ± 3.8 (25.6 -44.7)
PaO_2, mmHg	55.2 ± 3.4†‖(49.0 -58.8)	70.8 ± 8.4†§(62.0 -87.0)	55.6 ± 4.0†(48.0 -59.1)	79.3 ± 9.3 (60.0 -100)
HCO_3, mmoL/L	30.6 ± 1.7†§(28.6 -34.4)	31.4 ± 3.8†§(26.9 -39.6)	27.2 ± 1.7*(24.3 -29.2)	24.4 ± 1.9 (18.6 -31.2)
SaO_2%	86.6 ± 3.3†(80.4 -91.0)	92.2 ± 2.6†§(86.5 -96.3)	87.8 ± 3.5†(81.5 -92.5)	95.3 ± 1.6 (90.2 -98.3)
pH	7.35 ± 0.02†‡(7.32 -7.39)	7.35 ± 0.03†§(7.29 -7.41)	7.39 ± 0.02 (7.36 -7.42)	7.39 ± 0.03 (7.31 -7.55)
$PvCO_2$, mmHg	58.1 ± 4.3†§(49.6 -62.9)	58.1 ± 9.4†§(48.7 -82.2)	46.5 ± 2.9(42.1 -51.0)	42.4 ± 4.2 (26.7 -54.2)
PvO_2, mmHg	36.1 ± 2.1*(32.0 -39.0)	38.7 ± 3.3*(34.0 -49.0)	33.8 ± 3.0†(31.0 -40.0)	39.7 ± 4.3(31.3 -68.0)
HCO_3, mmoL/L	32.3 ± 1.6†§(29.3 -35.3)	32.2 ± 4.6†§(24.9 -42.4)	28.2 ± 1.6*(26.0 -31.0)	25.5 ± 2.1 (18.7 -36.0)
SvO_2 %	64.7 ± 3.9†(56.2 -69.8)	67.8 ± 5.5†(53.0 -77.5)	63.7 ± 4.2†(59.5 -72.2)	72.9 ± 5.4 (58.1 -93.4)
CO, l/min	4.42 ± 1.06(2.86 -6.40)	4.99 ± 1.56 (3.00 -9.31)	4.87 ± 1.14 (2.87 -6.50)	5.40 ± 1.66 (2.29 -12.60)
CI, l/min/m^2	3.44 ± 1.32 (1.63 -6.85)	3.39 ± 0.86 (1.80 -5.31)	3.22 ± 0.68 (2.23 -4.29)	3.36 ± 0.92 (2.15 -6.76)
Pam, mmHg	21.0 ± 3.9†(17.0 -31.0)	21.3 ± 4.7†(13.0 -32.0)	19.5 ± 7.6†(13.0 -36.0)	14.4 ± 3.9 (7.0 -31.0)
PAR, dyne· sec· cm^{-5}	274.4 ± 89.7†(151.2 -391.2)	237.5 ± 102.1†(32.4 -389.6)	224.4 ± 140.9†(98.5 -473.9)	123.7 ± 70.1 (16.2 -412.5)
TPR,dyne· sec· cm^{-5}	390.9 ± 109.9†(233.7 -530.0)	364.3 ± 108.3†(163.3 -545.5)	334.5 ± 137.5†(184.4 -557.5)	229.5 ± 89.3 (82.4 -556.0)
PAWP, mmHg	6.27 ± 1.79 (4.00-9.00)	7.37 ± 2.29 (4.00 -12.00)	6.75 ± 3.62 (2.00 -12.00)	6.55 ± 2.36 (0.00 -15.00)
Hb, g/dl	14.3 ± 1.7 (11.3 -17.6)	13.2 ± 1.8 (8.8 -15.0)	14.1 ± 1.3 (12.2 -15.7)	13.6 ± 1.7 (8.9 -17.6)
%VC, %	55.8 ± 20.0†(26.7 -96.6)	54.1 ± 27.9†(24.3 -108.0)	69.7 ± 11.6*(51.4 -86.0)	93.7 ± 21.6(43.7 -148.3)
%FEV1,%	35.3 ± 10.8†(20.1 -59.6)	49.4 ± 25.0†(14.9 -96.9)	47.0 ± 22.1†(23.9 -92.0)	74.2 ± 23.0 (18.6 -151.0)
FEV1%, %	0.48 ± 0.21†(0.26 -0.89)	0.61 ± 0.23 (0.18 -0.97)	0.50 ± 0.23*(0.30 -0.92)	0.69 ± 0.18 (0.20 -0.99)

* = $P < 0.05$ vs ncnx, † = $P < .01$ vs ncnx, ‡ = $P < 0.05$ vs ncHX, § = $P < 0.01$ vs ncHX, || = $P < 0.01$ vs HCnx.
The data are expressed as mean ± standard deviation. HCHX, hypercapnic hypoxia; HCnx, hypercapnic normoxia; ncHX, normocapnic nypoxia; ncnx, normocapnic normoxia; COPD, chronic obstructive pulmonary disease; TBsq, tuberculosis sequelae; DPB, diffuse pulmonary bronchiolitis; BE, bronchial ectasis; IP, interstitial pneumonitis; BMI, body mass index; CO, cardiac output; CI, cardiac index; PAm, mean pulmonary arterial pressure; PAR, pulmonary artery resistance; TPR, total pulmonary vascular resistance; PAWP, pulmonary arterial wedge pressure; VC, vital capacity; FVC, forced vital capacity; FEV1%, the ratio of forced expiratory volume in one second divided by FVC.

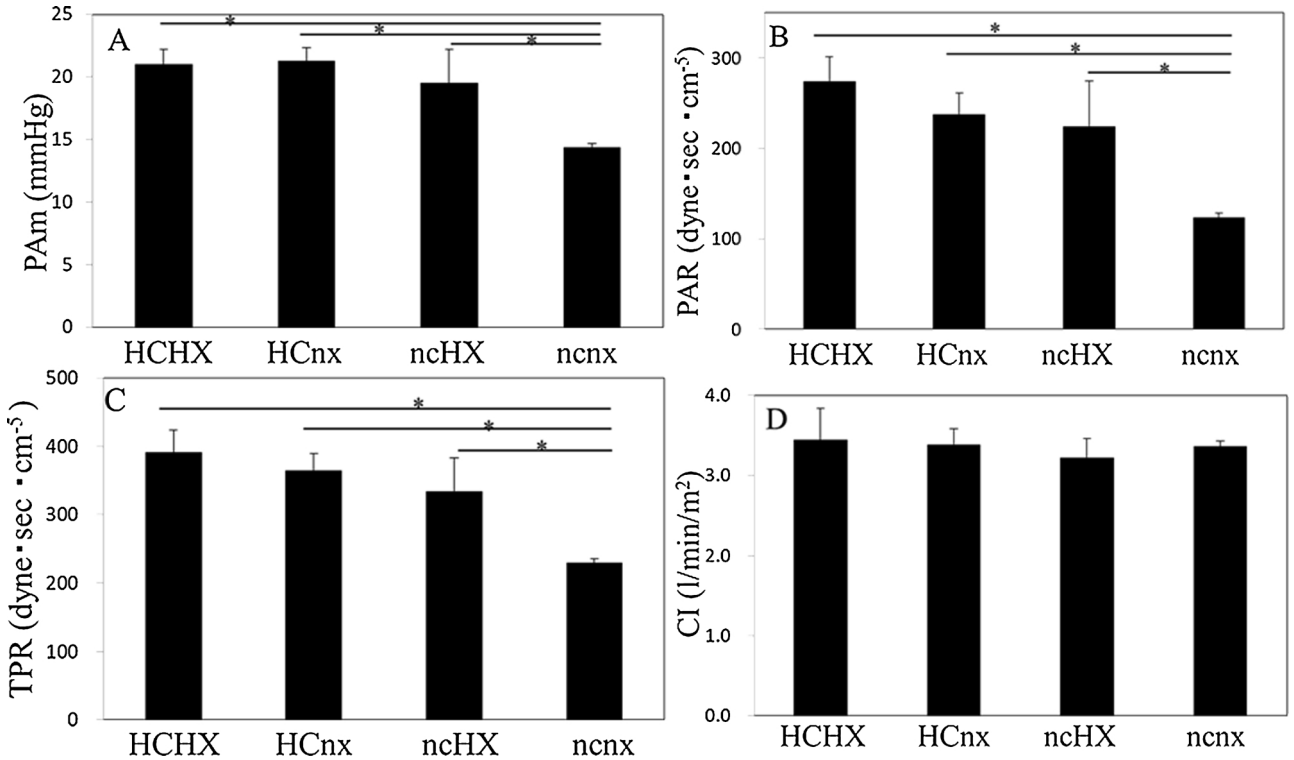

Fig. 2. Right heart catheterization parameters amongst the four groups. (A) PAm (mean pulmonary arterial pressure), (B) PAR (pulmonary artery resistance), (C) TPR (total pulmonary vascular resistance) and (D) CI (cardiac index). HCHX, Hypercapnic Hypoxia; HCnx, Hypercapnic Normoxia; ncHX, Normocapnic Hypoxia; ncnx, Normocapnic Normoxia. The data in each bar graph shows the mean and standard deviation. *, $P < .01$ vs ncnx.

baseline demographic and characteristics of the patients in the four groups. Fig. 2 describes the representative parameters. Compared with ncnx, PAm, PAR and TPR all showed significantly elevated levels in HCHX (ncnx vs HCHX, PAm / PAR / TPR, 14.4 ± 3.9 mmHg vs 21.0 ± 3.9 mmHg, $p < 0.01$/ 123.7 ± 70.1 dyne·s·cm^{-5} vs 274.4 ± 89.7 dyne·s·cm^{-5}, $p < 0.01$/ 229.5 ± 89.3 dyne·s·cm^{-5} vs 390.9 ± 109.9 dyne·s·cm^{-5}, $p < 0.01$), HCnx (ncnx vs HCnx, PAm / PAR / TPR, 14.4 ± 3.9 mmHg vs 21.3 ± 4.3 mmHg, $p < 0.01$ / 123.7 ± 70.1 dyne·s·cm^{-5} vs 237.5 ± 102.1 dyne·s·cm^{-5}, $p < 0.01$ / 229.5 ± 89.3 dyne·s·cm^{-5} vs 364.3 ± 108.3 dyne·s·cm^{-5}, $p < 0.01$) and ncHX (ncnx vs ncHX, PAm / PAR / TPR, 14.4 ± 3.9 mmHg vs 19.5 ± 7.6 mmHg, $p < 0.01$ / 123.7 ± 70.1 dyne·s·cm^{-5} vs 224.4 ± 140.9 dyne·s·cm^{-5}, $p < 0.01$ / 229.5 ± 89.3 dyne·s·cm^{-5} vs 334.5 ± 137.5 dyne·s·cm^{-5}, $p < 0.01$) with no difference amongst the three groups. There was no significant difference between PAWP, CO and CI amongst the four groups. Compared with ncnx,% VC and %FEV1 showed a significant decrease in HCHX (ncnx vs HCHX, %VC / %FEV1, 93.7 ± 21.6 % vs 55.8 ± 20.0 %, $p < 0.01$ / 74.2 ± 23.0% vs 35.3 ± 10.8%, $p < 0.01$), HCnx (ncnx vs HCnx, %VC / %FEV1, 93.7 ± 21.6% vs 54.1 ± 27.9%, $p < 0.01$/ 74.2 ± 23.0 % vs 49.4 ± 25.0 %, $p < 0.01$) and ncHX (ncnx vs ncHX, %VC / %FEV1, 93.7 ± 21.6 % vs 69.7 ± 11.6%, $p < 0.01$/ 74.2 ± 23.0% vs 47.0 ± 22.1 %, $p < 0.01$). Both PAm and PAR showed significant positive correlation with $PaCO_2$ (PAm vs $PaCO_2$, $r = 0.28$, $p < .001$, PAR vs $PaCO_2$, $r = 0.28$, $p < .001$) and a negative correlation with PaO_2 (PAm vs PaO_2, $r = -0.38$, $p < .001$, PAR vs $PaCO_2$, $r = -0.36$, $p < .001$) (Fig. 3). Multiple regression analysis in the model, including arterial blood gas analysis and cardiac parameters showed that $PaCO_2$ as well as oxygen saturation (SaO_2) and CI are independent variables for PAm after the exclusion of collinearity characteristics (Table 2).

Table 2
Univariate and multivariate regression analysis of the arterial blood gas and cardiac output on mean pulmonary arterial pressure.

	Univariate		Multivariate (*R* square 0.35)		
Variable	Beta	*P*	Beta	*P*	VIF
pH	−0.002	< .001	−0.017	ns	1.608
$PaCO_{2,mmHg}$	0.650	< .001	0.206	.011	2.156
$PaO_{2,mmHg}$	−1.032	< .001	−0.015	Ns	3.684
$SaO_{2,\%}$	−0.336	< .001	−0.398	< .001	4.298
$CO_{,l/min}$	−0.007	ns	−0.209	ns	5.893
$CI_{,l/min/m2}$	0.020	ns	0.304	.023	5.195

PAm, mean pulmonary arterial pressure; CO, cardiac index; CI, cardiac index.

4. Discussion

The main findings of this study are as follows. The hypercapnic patients (HCHX, HCnx), regardless of whether they were simultaneously accompanied by hypoxia or not, showed a significant increase in PAm, PAR and TPR compared to the patients with ncnx. The parameter $PaCO_2$ showed a significant positive correlation to PAm, PAR and TPR. Multiple regression analysis showed that associated factors of PAm included $PaCO_2$, as well as SaO_2, after excluding the collinearity characteristics of blood gases parameters. Despite the possibility that the alveolar partial pressure of oxygen and/or acidosis have been widely known to cause an elevation of PAm due to pulmonary vasoconstriction, our results evaluated by multiple regression analysis still strongly suggest the contribution of hypercapnia as an important factor in regulation of PAm. In fact, the contribution of acidosis was very little in our study as shown in Table1.

The study of vasoconstrictor action of hypercapnia has been dated back to the 1970s in animals (Barer et al., 1970; Lodi and Viswanathan,

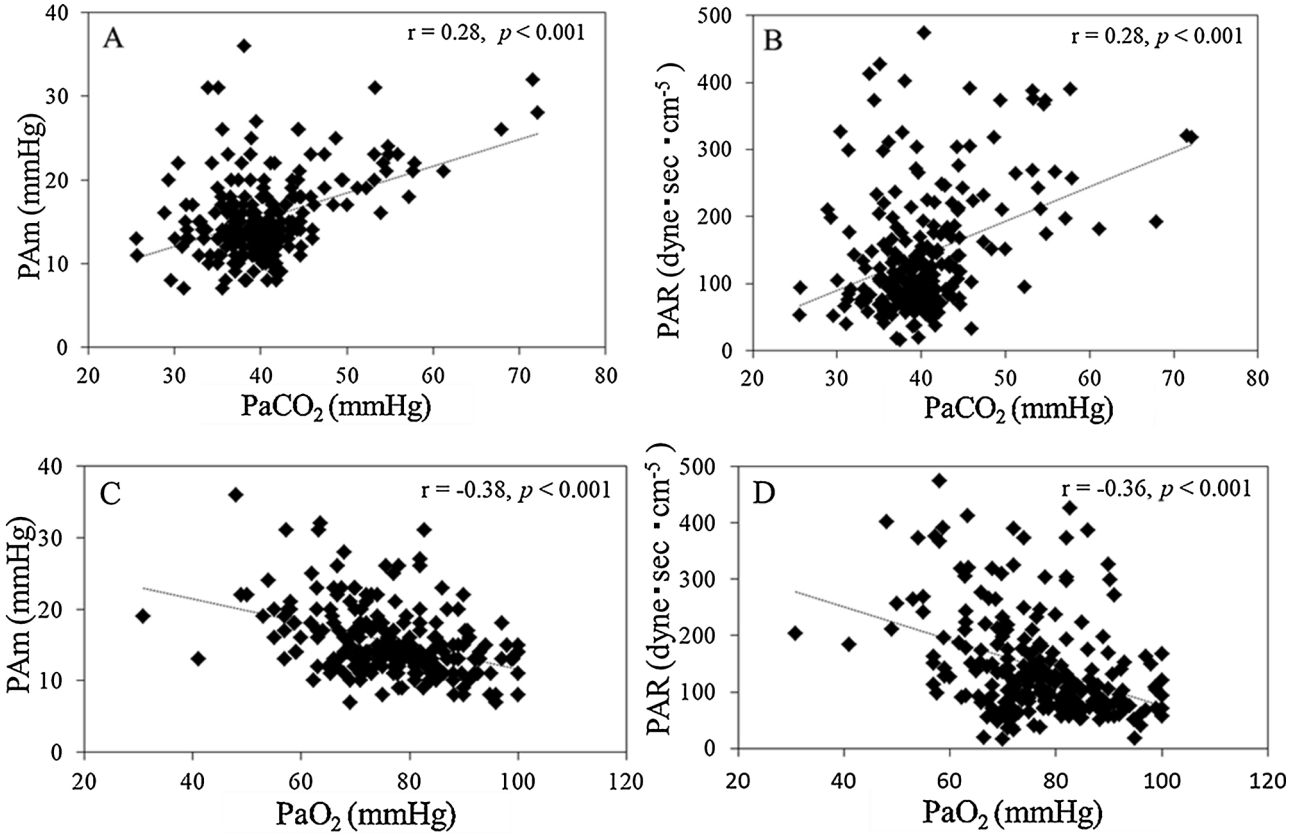

Fig. 3. Correlations between heart catheterization parameters and arterial blood gas analysis. (A) PAm and $PaCO_2$, (B) PAR and $PaCO_2$, (C) PAm and PaO_2, and (D) PAR and PaO_2. PAm, mean pulmonary arterial pressure; PAR, pulmonary artery resistance.

1974) and in humans (Kilburn et al., 1969; Viswanathan et al., 1976). More recently, study in human volunteers has demonstrated the marked pulmonary vasoconstrictor effect of hypercapnia and vasodilatory effect of hypocapnia (Balanos et al., 2003). The sensitivity of the pulmonary vasculature to carbon dioxide dominates over oxygen in regional vascular control in about half of the healthy human lung

(Dorrington et al., 2010). The main mechanism for sustained regional perfusion redistribution after the removal of HPV in subjects with unstable asthma has been strongly pointed out to be HCPV associated with hypoventilation (Kelly et al., 2017; Swenson, 2018; Dorrington et al., 2018).

The acute effect of a hypercapnic vasoconstriction has been suggested. The inhalation of 5 to 10% of CO_2 in isolated rat lung (Lee et al., 2003) and in humans (Kilburn et al., 1969; Viswanathan et al., 1976) for up to 20 min induced elevation of PAm as well as PAR with pH-independency and no change in either CO or PAWP. In other studies, PAm elevated to 0.59–0.85 mmHg per increase of 1 Torr $PaCO_2$ (Brimioulle et al., 1990) and to 0.4–1 mmHg per increase of 1 Torr $PaCO_2$ (Balanos et al., 2003; Kiely et al., 1996). As for the chronic effects of hypercapnia in patients with chronic pulmonary diseases, studies from Japan have reported a significant correlation of $PaCO_2$ with PAR and TPR in non-hypoxic and mildly hypercapnic patients (PaO_2 63 ~ 65.4 mmHg, $PaCO_2$ 47.6 ~ 48.7 mmHg) with COPD and tuberculosis sequelae (Yasuda et al., 1999; Furuya et al., 1983; Saito et al., 1999). We additionally revealed that hypercapnia was an independent risk to an increase of PAm. Previous work supports the pathological change of our study results that is the chronic hypercapnic effect on pulmonary circulation. Seven percent of CO_2 inhalation for six months in rats caused a significant increase to the medial thickness of muscular pulmonary arteries (Lodi and Viswanathan, 1974). Since no changes were observed either in the larger pulmonary arteries or in the pulmonary veins, the main mechanism has been suggested that CO_2 directly leads repeated constriction of the muscular pulmonary arteries. Collectively, these evidences suggest that hypercapnia may play a role for pulmonary vasoconstriction and vascular remodeling resulting in an elevation of PAm supporting a compatibility with our study results.

The level of PAm did not show any significant differences among HCHX, HCnx and ncHX, despite all showing higher PAm than ncnx in our study. An accurate appreciation of how CO_2 and O_2 stimuli act in synchrony or in opposition on pulmonary vessels is of importance. Croft et al. (2013) revealed the additive effect on human pulmonary vasoconstriction that the degree of pulmonary arterial pressure varied linearly with both alveolar partial pressures of carbon dioxide (end tidal PCO_2 levels from -9 to +6 mmHg from the baseline) and oxygen (end tidal PO_2 levels from 175 mmHg to 50 mmHg). While Baudouin SV et al (Baudouin and Evans, 1993) reported a dual effect in the rat lung. Normoxic hypercapnia (FiO_2 0.21, $PaCO_2$ = 60 ± 12 Torr) increased PAm mildly but significantly from 14 ± 2 mmHg to 15 ± 2 mmHg ($p < 0.05$) and hypoxic hypercapnia reduced this remarkably from 32 ± 2 mmHg to 27 ± 2 mmHg ($p < 0.01$). That is, this study shows hypercapnia cause a paradoxical vasodilator effect in the pulmonary vasculature and could damp any expected increase in PAm under severe hypoxia. This Baudouin study (Baudouin and Evans, 1992) was conducted in rats under acute condition and we compared the human arterial blood gas results directly with PAm under chronic condition. Nevertheless, a comparison between studies on a theoretical basis could be possible. Compared to those two previous studies, the level of hypercapnia in our HCHX group was similar whilst the level of hypoxia was not lower. Therefore, it is possible that hypercapnic paradoxical vasodilator effect less likely to occur in HCHX group. This may explain our similar high level of PAm in HCHX, HCnx and ncHX compared with ncnx.

Other mechanisms, except for alveolar hypoxia and/or HCPV in patients with chronic pulmonary diseases, may have contributed to an elevation of PAm in our results. COPD and tuberculosis accounted for most of the HCHX and HCnx groups. In both chronic pulmonary diseases, the decrease in pulmonary vascular bed caused by lung parenchymal destruction could occur. In fact, in the limited subjects who underwent a pulmonary function test including diffusing capacity, the subjects with hypercapnia (HCnx and HCHX) showed a significant decrease in the predictive diffusing capacity compared to ncnx (data not shown). Hypercapnia also induce cardiac acceleration through a sympathetic nerve system. Therefore the hypercapnic patients in chronic pulmonary diseases might have showed the elevation of PAm and PAR with having normal range of CI resulting from the pulmonary blood flow in the decreased pulmonary vascular bed. In addition, the impairment of endothelium-dependent pulmonary-artery relaxation which was found in end-stage chronic obstructive lung disease (Dinh-Xuan et al., 1991) might have contributed to an increase of PAm in our study as well. The 22 patients enrolled by Dinh-Xuan's study (Dinh-Xuan et al., 1991) showed not only obstructive pulmonary dysfunction (n = 22/22), but restrictive pulmonary dysfunction (n = 21/22) and hypercapnia (n = 16/22). Interestingly, 3 out of 22 patients showed hypercapnia without hypoxia.

Borderline elevation of PAm in our HCHX and HCnx groups at 21 ± 3.9 mmHg and 21.3 ± 4.3 mmHg respectively has recently been considered as a prognostic indicator (Kimura et al., 2012; Heresi et al., 2013; Douschan et al., 2018). The study showed that not only PAm but also %FVC was an independent determinant (Douschan et al., 2018). Those results might give us interpretation of the basic hypercapnia condition although it did not evaluate the blood gas analysis. There is a general 'oxycentric' and/or 'permissive hypercapnia' tendency in respiratory physiology and respiratory care to focus far more on oxygen than on carbon dioxide. However, one can make an argument to pursue the best $PaCO_2$ level considering the hypercapnic effect on pulmonary circulation, especially in chronic pulmonary diseases.

Our study had several limitations that we would like to acknowledge and address. Firstly, the small sample size and the retrospective aspect of our study might have had an effect on the results. Secondly, we were unable to enroll enough number of severe hypoxia patients because we excluded those already under LTOT. The oxygen and the carbon dioxide levels in the body are susceptible to changes by unstable supplemental oxygen uptake. Those subjects may not give an accurate representation of the precise and constant relationship between the pulmonary hemodynamics and the simultaneously obtained blood gas results. Thirdly, we enrolled several pulmonary physiology types in chronic pulmonary diseases such as restrictive, obstructive and mixed diseases. Although each pathophysiology may be different, it is well known that the patients with severe obstructive pulmonary disease often finally turned out to be mixed dysfunction by complicating with restrictive pulmonary dysfunction according to their disease progression. Nevertheless, the strength of our study was that we focused on the correlation between pulmonary hemodynamic measured precisely by RHC and presence of hypoxia and hypercapnia.

5. Conclusion

Our study suggest that chronic hypercapnia is complicatedly associated with the borderline elevation of PAm either by direct and/or indirect mechanisms such as HCPV, pulmonary blood flow in the decreased pulmonary vascular bed and the impairment of endothelium-dependent pulmonary-artery relaxation. Consideration by separating these effects out individually would be very difficult and our next step. In the case of severe pH accompanied by hypercapnia as well as hypoxia, aggressive treatment with non-invasive positive pressure ventilation should be considered in addition to supplemental oxygen. Further studies with a large enough sample size are required and warranted to establish the magnitudes of these interrelationships.

Disclosures

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