Analysis of Oxygenation in Chronic Thromboembolic Pulmonary Hypertension Using Dead Space Ratio and Intrapulmonary Shunt Ratio

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Summary

Current therapeutic methods for chronic thromboembolic pulmonary hypertension (CTEPH) can improve hemodynamic status and are expected to improve prognoses. However, some patients experience dyspnea during effort and continue supplemental oxygenation despite their hemodynamic status being fully improved. Considering the pathogenesis of CTEPH, the dead space and intrapulmonary shunt are assumed to be responsible for hypoxia in CTEPH, but their contributions are unclear. It is also unclear whether they are improved after treatment. The aim of this study was to investigate the implications of the dead space ratio (DSR) and the intrapulmonary shunt ratio (ISR) for hypoxia in CTEPH and treatment for CTEPH.

We retrospectively measured the DSR and ISR of 23 consecutive patients with CTEPH. For 11 of these 23 (10 were treated by balloon pulmonary angioplasty, one with riociguat), we also measured these parameters before and after CTEPH treatments. Overall, the DSR and ISR were abnormally elevated (DSR: 0.63 ± 0.06 ; ISR: 0.20 ± 0.05). After treatment, mean pulmonary artery pressure was improved (from 40.3 ± 8.1 to 25.5 ± 2.7 mmHg). Although atrial oxygen saturation (SaO_2), DSR and ISR were improved (SaO_2 : from 90.2 ± 3.2 to $93.7 \pm 1.8\%$; DSR: from 0.64 ± 0.06 to 0.58 ± 0.05 ; ISR: from 0.20 ± 0.04 to 0.18 ± 0.02), these improvements were slight compared with that of mean pulmonary artery pressure.

The DSR and ISR were abnormally elevated in patients with CTEPH and their improvement by treatment was limited. Only DSR can be a useful marker for normalization of hypoxia in CTEPH.

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Key words: Ventilation-perfusion mismatch, Oxygenation, Pulmonary embolism

The prognosis of chronic thromboembolic pulmonary hypertension (CTEPH) is markedly worse for patients with a mean pulmonary artery pressure (mPAP) more than 30 mmHg;^{1,2)} therefore, the first goal of treatment is to improve the mPAP so that it is less than 30 mmHg. The aim of additional therapies is to achieve an improvement in quality of life (QOL) if the patient is symptomatic.

The main symptom of CTEPH is dyspnea on exertion.^{3,4)} It is mainly caused by obstruction of the pulmonary arteries, which leads to an abnormal increase in pulmonary vascular resistance (PVR), which induces decreased cardiac output and right heart failure.⁵⁾ Currently, there are several methods of treatment that can result in improvement of pulmonary hypertension.⁶⁻⁸⁾ However, some patients have limitations in their activities due to residual hypoxia on exertion even though the mPAP is less than 25 mmHg.^{9,10)} This suggests that hypoxia contributes significantly to the symptoms and QOL of CTEPH patients whose hemodynamic status has fully improved. It

remains unclear how to normalize the oxygenation for patients with CTEPH.

With CTEPH, organized thrombi induce blood flow distribution abnormalities, which lead to various vasculopathy types.¹¹⁻¹³⁾ This induces ventricular-perfusion mismatch, which is the main cause of hypoxia in CTEPH. Pathological research of CTEPH has revealed that there are several types of vasculopathy associated with CTEPH that are determined according to the location of the organized thrombus;^{11,12)} on the other hand, it is etiologically divided into two types. One type is vasculopathy induced by blood overflow, which usually occurs in vessels without an organized thrombus. The other type is induced when there is no blood flow, which usually occurs in vessels distal to the organized thrombus. Both types demonstrate ventricular-perfusion mismatch; however, the mechanisms are totally different. Vasculopathy induced by blood overflow is similar to the pathological situation where an intrapulmonary shunt is used; vasculopathy without blood flow is similar to that where there is a dead

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Figure 1. Schema of measuring the dead space ratio and intrapulmonary shunt ratio. PeCO_2 indicates mixed-expired carbon dioxide.

space. These types of vasculopathy are considered to cause hypoxia in CTEPH; however, the extent to which they cause hypoxia is unclear. Furthermore, it is unclear if they are improved after treatment. The aim of this study was to investigate the implications of the dead space ratio (DSR) and the intrapulmonary shunt ratio (ISR) for hypoxia in CTEPH and treatment for CTEPH.

Methods

Study design: We performed a retrospective, observational study at the University of Tokyo Hospital to evaluate the mechanisms of hypoxia in CTEPH by calculating DSR and ISR. This study was approved by the University of Tokyo Hospital Review Board for clinical research (No. 2650), and all patients provided written informed consent before they were enrolled.

Patients: This study was conducted between November 2013 and May 2015 at the University of Tokyo Hospital in Japan. A total of 23 patients, including 2 with chronic thromboembolic disease and 21 with CTEPH, were enrolled, and their hemodynamic status, DSR, ISR, and respiratory function were measured. These parameters were also measured after treatment in 11 patients. All patients older than 18 years with CTEPH were considered for inclusion. Patients were excluded if they refused or were unable to participate, had other causes of pulmonary hypertension (i.e., collagen disease or congenital heart disease) or chronic lung disease, or required mechanical ventilation.

Hemodynamic status and respiratory function measurements: All parameters of hemodynamic status were measured in the catheter laboratory using a right heart catheter. Cardiac output was measured using the thermodilution method. Patients were placed in the supine position without supplemental oxygenation. Respiratory functional values were measured in the physiological laboratory at approximately the same time as when the right heart catheter test was performed.

Dead space ratio measurements: We measured the DSR using volumetric capnography (NICO Cardiopulmonary

Management System; Novametric; Wallingford, CT, USA) to calculate the partial pressure of mixed-expired carbon dioxide (PeCO_2) according to previous reports.¹⁴⁻¹⁶ Using PeCO_2 and partial pressure of arterial carbon dioxide (PaCO_2) measurements, which were obtained when PeCO_2 was measured, the DSR was calculated using the following equation:

$$\text{DSR} = (\text{PaCO}_2 - \text{PeCO}_2) / \text{PaCO}_2$$

Patients were examined in the supine position in the catheter laboratory. After inserting an arterial line in the right radial artery and a 7-Fr sheath in the right jugular vein, we measured baseline hemodynamic parameters using a right heart catheter. No patient was administered supplemental oxygenation. The patients wore a full face mask. Disposable mainstream flow, pressure, and a CO_2 sensor adapter (NICO) were placed at the airway opening. Patients were asked to relax. After wearing the mask and breathing through their mouth, we obtained an arterial blood sample; the variability rates of the expiratory volume and of the respiratory rate were $\leq 20\%$, and the variability of PeCO_2 was ≤ 1 mmHg within 2 minutes. We measured PeCO_2 when the arterial blood gas was measured (Figure 1). The normal range of DSR is from 0.2 to 0.35.

Intrapulmonary shunt ratio measurements: The ISR was calculated during oxygen loading (15 L/minute for 10 minutes) using the following equation:

$$\text{ISR} = (0.003 \cdot A\text{-aDO}_2) / (0.003 \cdot A\text{-aDO}_2 + \text{CaO}_2 - \text{C}\bar{\text{v}}\text{O}_2)$$

where $A\text{-aDO}_2$ indicates the alveolar-arterial oxygen difference, CaO_2 indicates the arterial oxygen content, and $\text{C}\bar{\text{v}}\text{O}_2$ indicates the oxygen content in mixed venous blood. The normal range of ISR is from 0.02 to 0.05.

Balloon pulmonary angioplasty: We performed balloon pulmonary angioplasty (BPA) in some patients in order to improve their hemodynamic status. BPA was performed according to previous reports.⁷ Some patients were administered riociguat to improve hemodynamic status.

Statistical analysis: To determine the mechanism of hypoxia in CTEPH, the DSR and ISR were calculated. Variations of these factors before and after treatment were

Table I. Patient Characteristics

Variable	
Number	23
Age	63.7 ± 11.8 (41.9 — 82.1)
Female (%)	16 (70)
Chronic thromboembolic disease (%)	2 (9)
WHO functional class	II (10), III (13)
Treatment	PEA (3), BPA (14), other (6)
Smoking	5 (22)
Average of Brinkman Index	312.0 ± 188.7 (120 — 640)
BNP (pg/mL)	102.0 ± 158.5 (4.0 — 656.9)
Systolic PAP (mmHg)	62.4 ± 20.5 (32 — 105)
Mean PAP (mmHg)	35.9 ± 10.5 (19 — 55)
PVR (Dyne/second/cm ⁵)	525.1 ± 244.9 (160 — 1023)
Cardiac index (L/minute/m ²)	2.7 ± 0.5 (1.8 — 3.7)
SaO ₂ (%)	91.5 ± 3.3 (84.0 — 97.5)
SvO ₂ (%)	66.8 ± 6.5 (49.7 — 81.1)
%VC (%)	103.0 ± 16.8 (80.5 — 134.0)
FEV1.0% (%)	79.8 ± 10.7 (68.6 — 114.2)
%DLCO (%)	83.8 ± 11.2 (60.7 — 102.2)
%RV (%)	84.9 ± 12.9 (57.2 — 103.5)
A-aDO ₂ (Torr)	39.2 ± 11.8 (1.7 — 55.0)

%VC indicates vital capacity percentage; %RV, residual volume percentage; A-aDO₂, alveolar-arterial oxygen difference; BNP, brain natriuretic peptide; %DLCO, carbon monoxide diffusing capacity as percent of predicted; FEV1.0%, forced expiratory volume % in one second; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SaO₂, arterial oxygen saturation; SvO₂, mixed-venous oxygen saturation; and WHO: World Health Organization.

Table II. Results of the Dead Space Ratio and Intrapulmonary Shunt Measurements

	Mean ± SD	(minimum—maximum)
Dead space ratio	0.63 ± 0.06	(0.51 — 0.75)
Intrapulmonary shunt ratio	0.20 ± 0.05	(0.11 — 0.36)

SD indicates standard deviation.

also measured. The results are presented as the mean ± standard deviation (SD). A comparison between the two groups was performed using a paired two-tailed *t*-test and the Wilcoxon signed rank test. *P* < 0.05 was considered statistically significant. Correlations between each parameter were determined using Pearson's product-moment correlation coefficient or the Spearman-rank method. All statistical analyses were performed using Prism 7 for Windows (version 7.03; GraphPad, San Diego, CA, USA).

Results

Baseline characteristics: Baseline characteristics of the patients are shown in Table I. The average mPAP and PVR were 35.9 ± 10.5 mmHg and 525.1 ± 244.9 dynes, respectively. Regarding oxygenation, the average arterial oxygen saturation (SaO₂) and A-aDO₂ were 91.5 ± 3.3% and 39.2 ± 11.8 Torr, which were not within the normal ranges. Five patients had a history of smoking; however, the maximum Brinkman index was 640. Twenty-one patients were diagnosed with CTEPH; of these 23 patients, 3 underwent pulmonary endarterectomy, 14 BPA, and 3 were administered riociguat.

Results of mechanism of hypoxia in CTEPH using dead space ratio and intrapulmonary shunt ratio: The

results of DSR and ISR measurements are shown in Table II. They were not within their normal ranges. For 11 of 23 patients (10 patients were treated by BPA, one with riociguat), we measured hemodynamic and respiratory status, including the DSR and ISR, before and after treatment (Figure 2). The median follow-up duration was 175 days. After treatment, mPAP, PVR, SaO₂, and A-aDO₂ were significantly improved compared with their values before treatment (mPAP: from 40.3 ± 8.1 to 25.5 ± 2.7 mmHg; PVR: from 612.9 ± 241.6 to 318.8 ± 76.1 dynes; SaO₂: from 90.2 ± 3.2 to 93.7 ± 1.8%; A-aDO₂: from 41.6 ± 8.9 to 32.3 ± 5.8 Torr); however, SaO₂ and A-aDO₂ did not improve to within the normal limits despite the mPAP being improved to approximately 25 mmHg. The DSR was significantly improved after treatment, whereas the ISR was improved, although the difference was not statistically significant (DSR: from 0.64 ± 0.06 to 0.58 ± 0.05; ISR: from 0.20 ± 0.04 to 0.18 ± 0.02). However, their values were not within their normal ranges any more than SaO₂ and A-aDO₂.

We also calculated the correlation of SaO₂ and other hemodynamic and respiratory parameters including the DSR and ISR. Only the DSR was significantly correlated with SaO₂ (Figure 3).

Figure 2. Parameters before and after treatment. A-aDO₂ indicates alveolar-arterial oxygen difference; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; and SaO₂, arterial oxygen saturation.

Figure 3. Correlation of arterial oxygen saturation and dead space ratio. SaO₂ indicates arterial oxygen saturation.

Discussion

Our data revealed that the DSR and ISR were abnormally elevated in CTEPH and in spite of mPAP improvement, these improvements were only slight in comparison to the improvement in oxygenation such as SaO₂ and A-aDO₂. There are 3 possible hypotheses for explaining the only slight improvement in oxygenation indices including DSR and ISR. The first is that the vessel which may have been responsible for oxygenation and the target of treatment are different. Oxygenation occurs in capillary vessels, and CTEPH includes various types of microvessel vasculopathies.¹²⁾ Current invasive therapies such as pulmonary endarterectomy and BPA, which are considered

curative therapeutic methods for CTEPH, target more proximal vessels.^{6,7,17)} There can be situations in which proximal vessels are fully treated to normalize the patient's hemodynamic status; however, vasculopathy in the distal vessels such as the capillary artery may remain. The second hypothesis was the involvement of inflammation in the pathogenesis of CTEPH. Generally, inflammation has important implications in the pathogenesis of CTEPH.^{11,18)} It has been revealed that several cytokines are related to the pathogenesis and progression of CTEPH. The secretion of IP-10 is related to poor pulmonary hemodynamics and physical capacity in CTEPH, and it might be involved in the pathological mechanism of PEA tissue formation.¹⁹⁾ Furthermore, there are several oxygenation processes in the lungs, such as ventilation, diffusion, and adequate blood flow to the capillary arteries; however, CTEPH treatment only improves the blood flow of capillary arteries. Therefore, if other oxygenation processes are impaired due to inflammation, then oxygenation will not normalize when only the delivery of blood flow to the capillary arteries is treated. The third is concerning technical issues related to BPA. The BPA technique has been currently refined. A small balloon (1.5 to 2.5 mm) is used during the initial session for each lung, regardless of the lesion diameter, and as many target lesions as possible are treated.²⁰⁾ Pulmonary arteries distal to the dilated sites were spontaneously enlarged,²¹⁾ and we dilated the same lesions using a balloon of adequate size at least 1 month after the initial session, which can be effective for normalizing ventricular-perfusion mismatch. However, from 2013 to 2015, we performed BPA by the conventional strategy, which is complicated because the balloon size was determined based on the vessel diameter measured during in-

travascular ultrasound imaging. Therefore, it is possible that the number of blood vessels to be treated might not be necessarily sufficient to normalize the DSR and ISR. From the perspective of normalizing ventricular-perfusion mismatch, the most important step is dilating all vessels equally. Unequal vessel dilatation leads to differences in the resistance of each blood vessel, deteriorating the balance of the blood flow distribution.

The DSR was significantly improved. The essence of current treatment for CTEPH is recanalization of vessels distal to the obstruction. In CTEPH, a lack of blood flow in the vessels distal to the obstruction contributes to the dead space, which is the volume of a breath that does not participate in gas exchange. Thus, current treatment for CTEPH directly results in improving the dead space, which leads to amelioration of gas exchange and oxygenation. This is one of the reasons DSR was correlated with SaO₂. However, the ISR was not significantly improved after treatment. This is because the venous admixture-like effects deteriorated the ISR. Venous admixture-like effects occur when the blood flow is large compared to the capacity of alveolar ventilation and some blood passes via the gas exchange but does not make contact with the alveolar air and flows into the left atrium as venous blood. If treatment is not sufficient, then vascular resistance varies in each blood vessel; therefore, there is a possibility that the blood flow distribution will become more unequal. In these cases, ventilation-perfusion mismatch deteriorates due to venous admixture-like effects. Therefore, the ISR could be one of the parameters of ventricular-perfusion mismatch in patients with CTEPH. A further decrease in mPAP and/or technical improvement to achieve normalization of DSR and ISR may be required for normalizing oxygenation in CTEPH.

Our study has one main limitation - the number of enrolled patients was small. This may have resulted in the finding that ISR improvement did not reach statistical significance. The DSR could be correlated with hypoxia in CTEPH. Furthermore, the DSR can be a useful marker for normalization of hypoxia in CTEPH.

Disclosures

Conflicts of interest: None.

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