Effects of pulmonary endarterectomy on pulmonary hemodynamics in chronic thromboembolic pulmonary hypertension, evaluated by interventricular septum curvature

Takahiko Saito, Hajime Kasai, Toshihiko Sugiura, Yukiko Takahashi, Hiroshi Tajima, Ayako Shigeta, Seiichiro Saka, Nobuhiro Tanabe and Koichiro Tatsumi

School of Medicine, Chiba University, Chiba, Japan; Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan

Abstract
The interventricular septum curvature, measured in images of electrocardiogram-gated 320-slice multidetector computed tomography, is reportedly useful and less invasive than right heart catheterization, as it could provide clues regarding pulmonary arterial pressure in patients with chronic thromboembolic pulmonary hypertension. Although pulmonary endarterectomy is an efficient treatment for chronic thromboembolic pulmonary hypertension, the interventricular septum curvature in patients who have received pulmonary endarterectomy has not been evaluated. We evaluated whether the interventricular septum curvature on electrocardiogram-gated 320-slice multidetector computed tomography can predict pulmonary hemodynamics in chronic thromboembolic pulmonary hypertension even after pulmonary endarterectomy. We studied 40 patients with chronic thromboembolic pulmonary hypertension (60.5 ± 9.7 years; 30 females), who underwent pulmonary endarterectomy at Chiba University Hospital between December 2010 and July 2018. To measure the interventricular septum curvature, we prepared left ventricular short-axis tomographic images from 4D images of electrocardiogram-gated 320-slice multidetector computed tomography. We calculated the radius of interventricular septum and determined the interventricular septum curvature in both the systolic and diastolic phases. We compared the interventricular septum curvature with pulmonary hemodynamics measured by right heart catheterization before and after pulmonary endarterectomy. After pulmonary endarterectomy, the correlations of the interventricular septum curvature with mean pulmonary arterial pressure, systolic pulmonary arterial pressure, and pulmonary vascular resistance disappeared, although the interventricular septum curvature was correlated with these pulmonary hemodynamic parameters before pulmonary endarterectomy. Changes in systolic interventricular septum curvature revealed significant correlations with changes in mean pulmonary arterial pressure, systolic pulmonary arterial pressure and pulmonary vascular resistance. Diastolic interventricular septum curvature also showed significant correlations with preoperative pulmonary hemodynamics, but not with postoperative pulmonary hemodynamics. Changes in the interventricular septum curvature after pulmonary endarterectomy could estimate the efficacy of pulmonary endarterectomy, although the interventricular septum curvature after pulmonary endarterectomy showed no significant correlations with pulmonary hemodynamics. Additionally, our findings confirmed that the interventricular septum curvature before pulmonary endarterectomy could be used to evaluate the severity of disease.

Keywords
interventricular septum curvature, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, computed tomography

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Corresponding author:
Hajime Kasai, Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan.
Email: daikasai6075@yahoo.co.jp

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by unresolved thrombi and vascular remodeling, leading to increased pulmonary vascular resistance (PVR), high pulmonary arterial pressure, and right ventricular (RV) failure. Advanced CTEPH leads to cardiac remodeling, involving RV dilatation and hypertrophy, tricuspid regurgitation, and depression of the interventricular septum (IVS), with further impacts on cardiac function. For patients with CTEPH who have surgically accessible thrombi, pulmonary endarterectomy (PEA) is the therapy of choice. Additionally, to qualitatively and quantitatively measure morphological changes in CTEPH, echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) are generally used. Abnormal IVS position and motion have been noted in patients with RV pressure overload. Leftward flattening of the IVS is a sensitive marker for RV systolic hypertension. In routine clinical practice, although IVS flattening in echocardiography indicates the presence of pulmonary hypertension (PH), visual assessment is generally used as the primary evaluation method. The IVS curvature (IVSC) is a parameter used to quantify the IVS configuration; this is measured by CT and MRI. The IVS and left ventricular eccentricity index have been used for qualitative evaluation of IVS flattening. Notably, the 2015 European Society of Cardiology and European Respiratory Society guidelines suggested the use of prespecified echocardiographic variables, including flattening of the IVS, as well as the tricuspid regurgitation peak gradient.

State-of-the-art multidetector CT (MDCT) scanners are now widely available and permit rapid acquisition of a thin-slice dataset, even in breathless patients. A 320-slice MDCT provides 16-cm cranio-caudal coverage and volumetric imaging of the entire heart with a single gantry rotation. In addition, a series of two gantry rotations (double volume scan) in combination with an electrocardiogram (ECG) (known as ECG-gated 320-slice MDCT) can acquire simultaneous images of the pulmonary arteries and entire heart. Furthermore, because of advances in CT technology, ECG-gated MDCT has been used to image the heart with high spatial and temporal resolution. The IVSC measured in ECG-gated 320-slice CT images is reportedly a useful and less invasive tool than right heart catheterization (RHC) for evaluation of pulmonary hemodynamics in patients with CTEPH.

PEA can improve pulmonary hemodynamics in patients with CTEPH. RV remodeling has been observed in patients with CTEPH; RV is almost completely restored after a hemodynamically successful PEA. Reesink et al. demonstrated that the severity of disease in CTEPH correlated with septal bowing four months after PEA. They also demonstrated that the change in septal bowing four months after PEA correlated with hemodynamic improvement. Although PEA is an efficient treatment for CTEPH, the IVSC in patients who previously underwent PEA has rarely been evaluated.

This study therefore aimed to evaluate whether the IVSC on ECG-gated 320-slice MDCT can predict pulmonary hemodynamics even after PEA and whether changes in the IVSC before and after PEA can predict changes in pulmonary hemodynamics in CTEPH.

Methods

Study population

The study group consisted of consecutive patients with a high clinical suspicion of CTEPH who underwent ECG-gated 320-slice MDCT and RHC from December 2010 to June 2018. All patients underwent PEA and had a confirmed diagnosis of CTEPH. Moreover, ECG-gated 320-slice MDCT and RHC were performed before PEA and approximately one year after PEA. The study was approved by the ethics committee of Chiba University (approval number 826). Written informed consent to use their examination results in future studies was obtained from each patient before they underwent CT and RHC.

Enhanced ECG-gated 320-slice CT

All CT scan results were obtained retrospectively from enhanced ECG-gated volume scanning using 320-slice MDCT (Aquilion One, Toshiba Medical, Tochigi, Japan) with a slice thickness of 0.5 mm and 0.35 s/rotation. To acquire simultaneous images of the pulmonary arteries and the entire heart, an axial series was performed comprising two gantry rotations in a cranio-caudal direction (double volume scan). The resulting dual-volume datasets were automatically stitched. Because the most cranial and caudal parts of each volume dataset (1.6 cm each) were not used to create images, the effective scan length was 25.6 cm. The tube voltage and current were set at 120 kV and 580 mA, respectively, using tube current dose modulation. By using a mechanical injector (Dual Shot, Nemoto, Tokyo, Japan), 100 mL of contrast media (Iomeron 350 mg/mL; Eisai, Tokyo, Japan) was injected at 3.5 mL/s. Then, the following saline–contrast mixture was injected: 40 mL of contrast media at 2.0 mL/s and 30 mL of saline at 1.5 mL/s. Time-resolved (per s) single-section CT scans were acquired at the level of the bifurcation of the pulmonary artery without breath hold. Ascending aortic time-resolved attenuation was then measured using the time-attenuation evaluation program accessible on the scanner. When the CT values in the ascending aorta had increased to 200 Hounsfield units (HU), we began the scan, and the patient was asked to perform breath holding.

IVSC on ECG-gated 320-slice CT

CT images were reconstructed at 5% intervals from 0% to 95% of the R–R interval. They were sent to a workstation (Ziostation2; Ziosoft Incorporated, Belmont, CA, USA)
that created cine images of the pulmonary arteries. Then, short-axis cine images of the heart were acquired using double-oblique multiplanar reformation. The IVSC was measured in the short-axis image plane at the midventricular level (papillary muscle visible). At this level, the cine image with the greatest deformation of the septum was used for quantification. We first marked two intersectional points of the midline of the left ventricular wall and extended lines of the right ventricular wall to the anterior and inferior sides. Next, the midpoint between these two points on the midline of the left ventricular wall was defined as the third point. Then, we read the X and Y coordinates of the three points. A circle that passed through the three points on the septum was used to calculate the radius of the septum. Finally, dividing one by the radius of the circle in cm, IVS bowing was quantified by the IVSC. A rightward (physiologic) curvature was denoted as a positive value and a leftward curvature as a negative value. The IVSC was measured at mediastinal window settings (level, 0 Hounsfield units (HU); width, 300 HU).

R: radius of the circle drawn by the ventricular septum.

that created cine images of the pulmonary arteries. Then, short-axis cine images of the heart were acquired using double-oblique multiplanar reformation. The IVSC was measured in the short-axis image plane at the midventricular level (papillary muscle visible). At this level, the cine image with the greatest deformation of the septum was used for quantification. We first marked two intersectional points of the midline of the left ventricular wall and extended lines of the right ventricular wall to the anterior and inferior sides. Next, the midpoint between these two points on the midline of the left ventricular wall was defined as the third point. Then, we read the X and Y coordinates of the three points. A circle that passed through the three points on the septum was used to calculate the radius of the septum. Finally, dividing one by the radius of the circle in cm, IVS bowing was quantified by the IVSC. A rightward (physiologic) curvature was denoted as a positive value and a leftward curvature as a negative value. The IVSC was measured at mediastinal window settings (level, 0 Hounsfield units (HU); width, 300 HU).

R: radius of the circle drawn by the ventricular septum.

Fig. 1. The method of calculating the interventricular septal curvature (IVSC). (a) Short-axis cine images of the heart were acquired using double-oblique multiplanar reformation. The IVSC was measured in the short-axis image plane at the midventricular level (papillary muscle visible). At this level, the cine image with the greatest deformation of the septum was used for quantification. We first marked two intersectional points of the midline of the left ventricular wall and extended lines of the right ventricular wall to the anterior and inferior sides. Next, the midpoint between these two points on the midline of the left ventricular wall was defined as the third point. (b) Then, we read the X and Y coordinates of the three points. (c) A circle that passed through the three points on the septum was used to calculate the radius of the septal curvature. (d) Finally, dividing one by the radius of the circle in cm, IVS bowing was quantified by the IVSC. A rightward (physiologic) curvature was denoted as a positive value and a leftward curvature as a negative value. The IVSC was measured at mediastinal window settings (level, 0 Hounsfield units (HU); width, 300 HU).

Fig. 2. Assessment of the intraventricular septal curvature (IVSC) in a 73-year-old woman. (Left) before pulmonary endarterectomy (PEA) (mean pulmonary arterial pressure (mPAP), 42 mmHg). The curvature was 0.143/cm. (Right) after PEA (mPAP, 23 mmHg). The curvature was 0.502/cm.

R: radius of the circle drawn by the ventricular septum.

RHC

A 7.5-French gauge Swan–Ganz thermodilution catheter (Edwards Lifesciences, Irvine, CA, USA) was inserted via the jugular approach. Pressure measurements were acquired from the superior vena cava, right atrium, right ventricle, and main pulmonary artery at end-expiration. The zero point was defined as mid-thoracic. Cardiac output (CO) was determined using the thermodilution method by averaging a minimum of three measurements. Left-to-right shunting was excluded by oximetry. PVR in Wood units (WU) was calculated using the equation: \( PVR = \frac{\text{mean pulmonary arterial pressure (mPAP) – pulmonary artery wedge pressure}}{\text{CO}} \).

Statistical analysis

Pearson correlation coefficients were used to assess the correlations of the hemodynamic data from RHC with the IVSC measured using ECG-gated 320-slice MDCT.
Correlation analyses of parameters with non-normal distributions were performed using Spearman correlation coefficients. The Wilcoxon signed-rank test was used to compare parameters between before and after PEA. To evaluate the quality and performance of the IVSC for predicting the mPAP (≥30 mmHg, ≥35 mmHg, and ≥38 mmHg) and the PVR (≥5.3 WU), receiver operating characteristic (ROC) curves were used. The thresholds of mPAP (≥38 mmHg) and PVR (≥5.3 WU (425 dynes s$^{-1}$ cm$^{-5}$)) were correlated with worse long-term survival after PEA. The area under the ROC curve (AUC), combining sensitivity and specificity, was used to assess the overall performance of the IVSC. The diagnostic potentials of the sIVSC and dIVSC for predicting mPAP over 30 mmHg, 35 mmHg, and 38 mmHg and PVR over 5.3 WU after PEA were also evaluated based on the cut-off values indicated by the ROC curve analysis before and after PEA. This area was interpreted as the average sensitivity value for all potential specificity values. All results are expressed as the mean ± standard deviation (SD), unless otherwise indicated. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the JMP 13.0 software (Cary, NC, USA).

Results

The study group comprised 40 consecutive patients (age, 60.5 ± 9.7 (SD) years; n = 30 females) with CTEPH diagnosed by RHC and CT and/or pulmonary angiography. Table 1 shows the baseline characteristics of the patients. The interval range between postoperative CT and PEA was 383.5 ± 44.0 days (251–520 days). Additionally, the interval ranges between CT and RHC, before and after PEA, were median five days (range, 0–23) and 2 (1–13), respectively. There were 14 patients with residual PH approximately one year after PEA. Regarding treatment, six patients who had used pulmonary vasodilators after PEA continued pulmonary vasodilator use. Additionally, four patients were administered pulmonary vasodilators after RHC one year after PEA. Three patients continued oxygen therapy without pulmonary vasodilators and one patient continued without treatment because this patient’s mPAP was approximately 25 mmHg.

Table 2 and 3 show the preoperative and postoperative pulmonary hemodynamics of the patients and correlation between hemodynamic data and the IVSC, respectively. Fig. 3 shows the IVSC before and after PEA. The sIVSC, mPAP, systolic pulmonary arterial pressure (sPAP), diastolic pulmonary arterial pressure (dPAP), and PVR were 0.150 ± 0.122 cm$^{-1}$, 43.8 ± 8.8 mmHg, 76.7 ± 16.7 mmHg, 10.4 ± 6.6 mmHg, and 8.8 ± 3.3 WU (before PEA/after PEA), respectively. After PEA, the mPAP, sPAP, dPAP, PVR, sIVSC, and dIVSC significantly improved. The sIVSC showed significant correlations with mPAP ($r = –0.635$, $p < 0.001$), sPAP ($r = –0.671$, $p < 0.001$), and PVR ($r = –0.678$, $p < 0.001$) before PEA, although these correlations disappeared after PEA. Changes in the sIVSC, mPAP, sPAP, dPAP, PVR, sIVSC, and dIVSC significantly improved. The area under the ROC curve (AUC) was used to assess the overall performance of the IVSC. The diagnostic potentials of the sIVSC and dIVSC for predicting mPAP over 30 mmHg, 35 mmHg, and 38 mmHg and PVR over 5.3 WU after PEA were also evaluated based on the cut-off values indicated by the ROC curve analysis before and after PEA. This area was interpreted as the average sensitivity value for all potential specificity values. All results are expressed as the mean ± standard deviation (SD), unless otherwise indicated. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the JMP 13.0 software (Cary, NC, USA).

Table 1. Baseline characteristics ($n = 40$).

| Parameter                  | Pre PEA | At the time of PEA | Post PEA |
|---------------------------|---------|-------------------|----------|
| Age (years)               | 60.5 ± 9.7 | 1.57 ± 0.09 | 1.59 ± 0.18 |
| Sex, n (female/male)      | 30/10   | 56.5 ± 10.8      |          |
| Body height (m)           | 1.57 ± 0.09 | 56.5 ± 10.8 | 60.5 ± 9.7 |
| Body weight (kg)          | 54.8 ± 9.4 | 56.5 ± 10.8 |          |
| Body surface area (m$^2$) | 1.57 ± 0.16 | 56.5 ± 10.8 |          |
| WHO functional class, n (%) | 0 (0.0 %) | 20 (50.0 %) |          |
| Treatment                | 25 (1–4 L/min) | 36 (1–6 L/min) | 27 (0.5–4 L/min) |
| Oxygen therapy, n         | 7 (17.5 %) | 8 (20.0 %) | 0 (0.0 %) |
| Oral prostaglandin I2, n (%) | 7 (17.5 %) | 8 (20.0 %) | 0 (0.0 %) |
| Intravenous prostaglandin I2, n (%) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
| Phosphodiesterase V inhibitor, n (%) | 9 (22.5 %) | 15 (37.5 %) | 1 (2.5 %) |
| Endothelin antagonist, n (%) | 9 (22.5 %) | 9 (22.5 %) | 1 (2.5 %) |
| Soluble guanylate cyclase stimulators, n (%) | 12 (30.0 %) | 11 (27.5 %) | 6 (15 %) |

PEA: pulmonary endarterectomy.

Note: Data are presented as mean ± standard deviation.
in sIVSC was significantly correlated with changes in the mPAP, sPAP, and PVR \((r = -0.584, p < 0.001; r = -0.675, p < 0.001; r = -0.703, p < 0.001, \text{ respectively})\). The dIVSC also showed a significant correlation with preoperative pulmonary hemodynamics, which had disappeared in the assessment of postoperative pulmonary hemodynamics.

The diagnostic potentials of the sIVSC and dIVSC for predicting mPAP over 30 mmHg, 35 mmHg, and 38 mmHg and PVR over 5.3 WU were evaluated by ROC curve analysis (Tables 4 and 5). For patients with mPAP values < 30 mmHg, the number of postoperative sIVSC measurements > 0.287 was 26/33 (specificity: 78.8%); for patients with mPAP values ≥ 30 mmHg, the number of postoperative sIVSC measurements ≤ 0.287 was 6/7 (sensitivity: 85.7%). For patients with mPAP values < 35 mmHg, the number of postoperative sIVSC measurements > 0.229 was 33/38 (specificity: 86.8%); for patients with mPAP values ≥ 35 mmHg, the number of postoperative sIVSC measurements ≤ 0.229 was 1/2 (sensitivity: 50.0%). For patients with mPAP values < 38 mmHg, the number of postoperative sIVSC measurements > 0.199 was 35/39 (specificity: 89.7%); for patients with mPAP values ≥ 38 mmHg, the number of postoperative sIVSC measurements ≤ 0.199 was 0/1 (sensitivity: 0%).

**Table 2.** Pulmonary hemodynamic data and IVSC \((n = 40)\).

| Parameter | Pre PEA | Post PEA | Difference | \(p\) Value |
|-----------|---------|----------|------------|-------------|
| **Pulmonary hemodynamic data** |         |          |            |             |
| mPAP (mmHg) | 43.8 ± 8.8 | 23.4 ± 6.6 | -20.4 ± 9.1 | <0.001 |
| sPAP (mmHg) | 76.7 ± 16.7 | 39.4 ± 10.4 | -37.3 ± 17.0 | <0.001 |
| dPAP (mmHg) | 20.8 ± 6.7 | 10.4 ± 4.0 | -10.4 ± 5.8 | <0.001 |
| PVR (Wood units) | 8.8 ± 3.3 | 3.5 ± 1.6 | -5.3 ± 3.2 | <0.001 |
| CO (L min\(^{-1}\)) | 4.3 ± 1.0 | 4.4 ± 0.9 | 0.1 ± 0.8 | 0.574 |
| CI (L min\(^{-1}\) m\(^{-2}\)) | 2.8 ± 0.7 | 2.7 ± 0.5 | -0.0 ± 0.5 | 0.957 |
| PAWP (mmHg) | 7.9 ± 3.0 | 8.6 ± 2.7 | 0.65 ± 3.0 | 0.175 |
| **IVSC** |         |          |            |             |
| Systolic (cm\(^{-1}\)) | 0.150 ± 0.122 | 0.323 ± 0.086 | 0.172 ± 0.111 | <0.001 |
| Diastolic (cm\(^{-1}\)) | 0.247 ± 0.054 | 0.283 ± 0.045 | 0.036 ± 0.054 | <0.001 |

mPAP: mean pulmonary arterial pressure; sPAP: systolic pulmonary arterial pressure; dPAP: diastolic pulmonary arterial pressure; PVR: pulmonary vascular resistance; CO: cardiac output; CI: cardiac index; PAWP: pulmonary artery wedge pressure; IVSC: interventricular septum curvature; PEA: pulmonary endarterectomy.

Note: Data are presented as mean ± standard deviation.

**Table 3.** Correlation between pulmonary hemodynamic data and curvature \((n = 40)\).

| Variables | mPAP | sPAP | dPAP | PVR | CO | CI |
|-----------|------|------|------|-----|----|----|
| Pre PEA |        |      |      |     |    |    |
| Systolic IVSC | \(r = -0.635\) | \(r = -0.671\) | \(r = -0.486\) | \(r = -0.678\) | \(r = 0.519\) | \(r = 0.538\) |
| \(p < 0.001\) | \(p < 0.001\) | \(p = 0.002\) | \(p < 0.001\) | \(p < 0.001\) | \(p < 0.001\) | \(p < 0.001\) |
| Diastolic IVSC | \(r = -0.461\) | \(r = -0.433\) | \(r = -0.289\) | \(r = -0.422\) | \(r = 0.277\) | \(r = 0.388\) |
| \(p = 0.003\) | \(p = 0.005\) | \(p = 0.071\) | \(p = 0.007\) | \(p = 0.084\) | \(p = 0.014\) | \(p = 0.014\) |
| Post PEA |        |      |      |     |    |    |
| Systolic IVSC | \(r = -0.266\) | \(r = -0.272\) | \(r = -0.130\) | \(r = -0.223\) | \(r = 0.010\) | \(r = 0.289\) |
| \(p = 0.098\) | \(p = 0.089\) | \(p = 0.424\) | \(p = 0.168\) | \(p = 0.953\) | \(p = 0.071\) | \(p = 0.071\) |
| Diastolic IVSC | \(r = -0.288\) | \(r = -0.284\) | \(r = -0.154\) | \(r = -0.161\) | \(r = 0.095\) | \(r = 0.021\) |
| \(p = 0.071\) | \(p = 0.076\) | \(p = 0.343\) | \(p = 0.322\) | \(p = 0.559\) | \(p = 0.897\) | \(p = 0.897\) |
| Difference | \(\Delta mPAP\) | \(\Delta sPAP\) | \(\Delta dPAP\) | \(\Delta PVR\) | \(\Delta CO\) | \(\Delta CI\) |
| \(\Delta\text{Systolic IVSC}\) | \(r = -0.584\) | \(r = -0.675\) | \(r = -0.482\) | \(r = -0.703\) | \(r = 0.394\) | \(r = 0.303\) |
| \(p < 0.001\) | \(p < 0.001\) | \(p = 0.002\) | \(p < 0.001\) | \(p = 0.012\) | \(p = 0.057\) | \(p = 0.057\) |
| \(\Delta\text{Diastolic IVSC}\) | \(r = -0.370\) | \(r = -0.396\) | \(r = -0.132\) | \(r = -0.363\) | \(r = 0.010\) | \(r = 0.030\) |
| \(p = 0.019\) | \(p = 0.011\) | \(p = 0.418\) | \(p = 0.022\) | \(p = 0.953\) | \(p = 0.854\) | \(p = 0.854\) |

mPAP = mean pulmonary arterial pressure; sPAP = systolic pulmonary arterial pressure; dPAP = diastolic pulmonary arterial pressure; PVR = pulmonary vascular resistance; CO = cardiac output; CI = cardiac index; PEA = pulmonary endarterectomy
was 0/1 (sensitivity: 0.0%). For patients with PVR values < 5.3 WU, the number of postoperative sIVSC measurements > 0.225 was 30/34 (specificity: 88.2%); for patients with PVR values ≥ 5.3 WU, the number of postoperative sIVSC measurements ≤ 0.225 was 2/6 (sensitivity: 33.3%).

**Discussion**

To the best of our knowledge, this is the first study to assess the ability of 320-slice MDCT to evaluate the IVSC in subjects with CTEPH who have undergone PEA. There were two main findings. First, the change in the IVSC after PEA could estimate the efficacy of PEA, although the IVSC after PEA showed no significant correlation with pulmonary hemodynamics. Second, the IVSC before PEA could be used to evaluate the severity of disease. Moreover, the IVSC could be used to assess the presence of moderate mPAP, even in patients with CTEPH who have undergone PEA.

**Relationship between change in the IVSC and changes in pulmonary hemodynamics**

In this study, the preoperative IVSC correlated with preoperative mPAP and PVR, as observed in a previous study. In addition, the amount of change in the sIVSC and dIVSC before and after PEA correlated with the amount of change in mPAP and PVR. However, the correlation of the IVSC with mPAP and PVR disappeared postoperatively. We previously reported that the IVSC measured by ECG-gated 320-slice MDCT correlates with sPAP and mPAP in patients with CTEPH before PEA; the results of the present study were consistent with those of our previous report. Other previous reports of changes in morphology and RV function after PEA in CTEPH patients, using various imaging modalities, have revealed that remodeling and RV dilatation improved after PEA. In particular, Reesink et al. used MRI to evaluate the IVSC before and after PEA and found that the IVSC could improve to the values recorded in healthy controls. Surie et al. reported that RV wall stress decreased significantly after PEA. However, they reported that, when measured by transthoracic echocardiography after PEA, systolic and diastolic RV function deteriorated and showed gradual, incomplete recovery over a one-year follow-up period. Of 40 patients, 29 underwent echocardiography within two days before RHC; in these patients, correlations between the IVSC and echocardiographic parameters could be evaluated. The

![Fig. 3. Visualized intraventricular septal curvature (IVSC) before and after pulmonary endarterectomy (PEA) (n = 40). The blue line and blue translucent area show the mean value of IVSC and the 95% confidence interval of IVSC.](image)

| Parameter | Cut-off value | Before PEA | After PEA |
|-----------|---------------|------------|-----------|
| mPAP ≥ 30 mmHg | | Sensitivity | Specificity | Sensitivity | Specificity |
| Systolic IVSC (cm⁻¹) | 0.287 | 91.9 % | 66.7 % | 85.7 % | 78.8 % |
| Diastolic IVSC (cm⁻¹) | 0.286 | 83.8 % | 100.0 % | 85.7 % | 66.7 % |
| mPAP ≥ 35 mmHg | | Sensitivity | Specificity | Sensitivity | Specificity |
| Systolic IVSC (cm⁻¹) | 0.229 | 76.5 % | 83.3 % | 50.0 % | 86.8 % |
| Diastolic IVSC (cm⁻¹) | 0.286 | 85.3 % | 66.7 % | 100.0 % | 60.5 % |
| mPAP ≥ 38 mmHg | | Sensitivity | Specificity | Sensitivity | Specificity |
| Systolic IVSC (cm⁻¹) | 0.199 | 76.7 % | 80.0 % | 0.0 % | 89.7 % |
| Diastolic IVSC (cm⁻¹) | 0.222 | 53.3 % | 90.0 % | 0.0 % | 87.2 % |
| PVR ≥ 5.3 WU | | Sensitivity | Specificity | Sensitivity | Specificity |
| Systolic IVSC (cm⁻¹) | 0.225 | 75.8 % | 85.7 % | 33.3 % | 88.2 % |
| Diastolic IVSC (cm⁻¹) | 0.222 | 51.5 % | 100.0 % | 88.2 % | 16.7 % |

mPAP: mean pulmonary arterial pressure; IVSC: interventricular septum; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; WU: Wood units.
sIVSC showed significant correlations with RV size ($p = 0.005$), pressure gradient of tricuspid regurgitation ($r = -0.407$, $p = 0.029$), and tricuspid annular plane systolic excursion ($r = -0.443$, $p = 0.016$) before PEA, although these correlations disappeared after PEA. While the sIVSC may be related to RV dilatation and systolic function, the IVSC and echocardiographic parameters may not be correlated because the IVSC was not correlated with pulmonary hemodynamics measured by RHC after PEA. Possible reasons for the postoperative disappearance of the correlations between the IVSC and pulmonary hemodynamics are as follows. First, in the present study, 14 patients with residual PH after PEA were included; notably, RV remodeling could not completely disappear in residual PH. Additionally, there is a possibility that the IVSC does not correlate with pulmonary artery pressure in patients who exhibit normal pulmonary artery pressure. Second, RV dysfunction caused by PEA may influence the IVSC. Ischemia, inflammation, and myocardial edema have been suggested; in patients with CTEPH, hypertrophied and dilated RV might be more sensitive to ischemia or other surgery-related injuries. Therefore, pressure overload in patients with CTEPH. The change in diIVSC before and after PEA ($0.150 \pm 0.122 \text{ cm}^{-1}$ vs. $0.323 \pm 0.086 \text{ cm}^{-1}$) was more prominent than that in diIVSC ($0.247 \pm 0.054 \text{ cm}^{-1}$ vs. $0.283 \pm 0.045 \text{ cm}^{-1}$) in this study. Although volume overload can lead to the D-shape septum becoming more pronounced at diastole, flattening of the septum is significant at systole, as patients with CTEPH are under pressure overload. Therefore, the pressure overload condition of patients with CTEPH could have led to the lesser change in diIVSC before and after PEA in this study. However, the IVSC can be affected by various factors such as remodeling of the right and left ventricular walls in addition to pressure and volume overload. As the parameters measured by RHC in this study did not represent volume overload, the significance of diIVSC in pulmonary hemodynamics could not be clarified. Further case accumulation and studies that focus on the diastolic phase are needed.

**IVSC in postoperative evaluation of PH**

The IVSC can be an indicator of improvement in postoperative pulmonary hemodynamics. When mPAP improves after

### Table 5. The relation between the cut off value of IVSC based on preoperative period and mPAP (≥ 30, 35, and 38 mmHg). PVR (≥ 5.3 Wood units) after PEA (n = 40).

| Parameter | mPAP < 30 mmHg (n = 33) | mPAP ≥ 30 mmHg (n = 7) |
|-----------|------------------------|------------------------|
| Systolic IVSC > 0.287, n (%) | 26 (96.3) | 1 (3.7) |
| Systolic IVSC < 0.287, n (%) | 7 (53.9) | 6 (46.1) |
| Diastolic IVSC > 0.286, n (%) | 22 (95.7) | 1 (4.3) |
| Diastolic IVSC ≤ 0.286, n (%) | 11 (64.7) | 6 (35.3) |
| mPAP < 35 mmHg (n = 38) | mPAP ≥ 35 mmHg (n = 2) |
| Systolic IVSC > 0.229, n (%) | 33 (97.1) | 1 (2.9) |
| Systolic IVSC < 0.229, n (%) | 5 (83.3) | 1 (16.7) |
| Diastolic IVSC > 0.286, n (%) | 23 (100.0) | 0 (0.0) |
| Diastolic IVSC ≤ 0.286, n (%) | 15 (88.2) | 2 (11.8) |
| mPAP < 38 mmHg (n = 39) | mPAP ≥ 38 mmHg (n = 1) |
| Systolic IVSC > 0.199, n (%) | 35 (97.2) | 1 (2.8) |
| Systolic IVSC < 0.199, n (%) | 4 (100.0) | 0 (0.0) |
| Diastolic IVSC > 0.222, n (%) | 34 (97.1) | 1 (2.9) |
| Diastolic IVSC ≤ 0.222, n (%) | 5 (100.0) | 0 (0.0) |
| PVR < 5.3 WU (n = 34) | PVR ≥ 5.3 WU (n = 6) |
| Systolic IVSC > 0.225, n (%) | 30 (88.2) | 4 (11.8) |
| Systolic IVSC < 0.225, n (%) | 4 (66.7) | 2 (33.3) |
| Diastolic IVSC > 0.222, n (%) | 30 (85.7) | 5 (14.3) |
| Diastolic IVSC ≤ 0.222, n (%) | 4 (80.0) | 1 (20.0) |

mPAP: mean pulmonary arterial pressure; IVSC: interventricular septum; PVR: pulmonary vascular resistance; WU: Wood units.
PEA, the postoperative IVSC also improves; this change in the IVSC could reflect change in pulmonary hemodynamics. Moreover, patients who exhibited improved IVSC, relative to the cut-off values that indicate mPAP ≥30 mmHg, ≥35 mmHg, and ≥38 mmHg, as well as PVR ≥5.3 WU, may also exhibit improvement of mPAP relative to the cut-off values. In contrast, patients who exhibited insufficient improvement in the IVSC, with respect to the cut-off value, did not consistently show lack of mPAP improvement. Therefore, in some postoperative cases, IVSC compression remains even after pressure is reduced. This indicates that morphological changes may remain after improvement of postoperative pulmonary hemodynamics. Thus, postoperative changes mentioned in the previous paragraph may be affected. Patients in whom IVSC compression remains after PEA may require RHC to evaluate whether residual PH continues to persist.

**CO and PVR in this study**

In this study, although patients before PEA had a high baseline PVR (8.8 WU), they also had a high baseline cardiac index (CI) (2.8 L min$^{-1}$ m$^{-2}$). In a retrospective analysis of data from long-term medical records of patients with CTEPH at our hospital, the mean CI was similar to that in the present study (CI: 2.9 ± 0.8 L min$^{-1}$ m$^{-2}$). The following factors could contribute to high CI in our institution. First, most patients could be early detection cases. Second, 22 of 40 patients had already been administered a pulmonary vasodilator, most often riociguat ($n=12$), before preoperative RHC. Indeed, in the five patients for whom pulmonary hemodynamics were compared between before and after administration of riociguat, mean CI increased from 2.35 ± 0.36 L min$^{-1}$ m$^{-2}$ to 2.87 ± 0.80 L min$^{-1}$ m$^{-2}$ (change: 0.52 ± 0.66 L min$^{-1}$ m$^{-2}$). In addition, inconsistency between the poor changes in CI (0.0 ± 0.5 L min$^{-1}$ m$^{-2}$) and the improvement in PVR (5.3 ± 3.2 WU) after PEA may have been caused by the distribution of CIs in our patients. Our patients included those with high CI and those with low CI. When patients were grouped depending on the lower limit of the normal value of CI (2.6 L min$^{-1}$ m$^{-2}$) (Supplemental Table 1), patients with low CI (CI ≤ 2.6 L min$^{-1}$ m$^{-2}$) and patients with high CI (> 2.6 L min$^{-1}$ m$^{-2}$) both showed decreases in mPAP and PVR. In contrast, CIs increased in patients with low CI, whereas CIs decreased in patients with high CI (changes in CI, 0.24 ± 0.29 vs. –0.32 ± 0.45 L min$^{-1}$ m$^{-2}$, $p < 0.001$). Due to the presence of these two groups, the mean CI value did not change after PEA.

**Study limitations**

This study had some limitations. First, it was a single-center retrospective study that included a small number of subjects. However, because CTEPH is rare, the present report could be noteworthy within this field. Second, the correlation between enhanced ECG-gated 320-slice MDCT parameters and RHC pulmonary hemodynamic data should ideally be studied by performing the two examinations on the same day; in our study, most patients underwent these two examinations within 25 days of each other.

**Conclusions**

In conclusion, in patients with CTEPH, the IVSC before PEA could be used to estimate mPAP and evaluate the severity of disease. Moreover, although the IVSC after PEA did not significant correlate with pulmonary hemodynamics, change in the IVSC after PEA may estimate the efficacy of PEA.

**Conflict of interest**

Toshihiko Sugiura works in an endowed department sponsored by Actelion Pharmaceuticals. Nobuhiro Tanabe works in an endowed department sponsored by Actelion Pharmaceuticals and has received research funding from Nippon Shinyaku and honoraria from Actelion Pharmaceuticals, Bayer, and Nippon Shinyaku. Koichiro Tatsumi has received remuneration from Actelion Pharmaceuticals and scholarship funds and donations from Pfizer. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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**Ethical approval**

This study was approved by the ethics committee of Chiba University, Japan (approval number 2584). Written informed consent was obtained from all patients who were enrolled since 2009, when this requirement became mandatory (approval number 826).

**Contributorship**

Takahiko Saito designed the study and wrote the initial draft of the manuscript. Hajime Kasai and Toshihiko Sugiura contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**ORCID iDs**

Takahiko Saito https://orcid.org/0000-0001-6275-4789
Ayako Shigeta https://orcid.org/0000-0002-9289-2901

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