Computed tomography angiographic parameters of pulmonary artery as prognostic factors of residual pulmonary hypertension after pulmonary endarterectomy

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Abstract

Objectives: This study aimed to retrospectively assess using computed tomography pulmonary angiography (CTPA) for predicting residual pulmonary hypertension (RPH) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary endarterectomy (PEA).

Methods: We retrospectively analyzed data of 131 patients with CTEPH who underwent PEA in our center (2008–2015). We measured several diameters of the pulmonary artery and thoracic aorta preoperatively. We evaluated the relationship between these measurements (and their indices) and signs of RPH represented by pulmonary artery systolic pressure (PASP) estimated by echocardiography.

Results: Significant correlations were observed between the aortopulmonary index and prediction of any residual hypertension and moderate/severe hypertension 1 year after PEA, and any residual hypertension and severe hypertension 2 years after PEA. The aortopulmonary index

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was significantly related to a reduction in PASP 1 year after the operation. A lower aortopulmonary index (≤0.88 for the ascending aorta and ≤0.64 for the descending aorta) predicted lower RPH.

Conclusions: Preoperative CTPA parameters can be used to assess the risk of RPH after PEA. The aortopulmonary index has significant predictive value for RPH and a reduction in PASP after PEA. Lower values of the aortopulmonary index suggest a better outcome after PEA.

Keywords
Chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, computed tomography angiography, residual pulmonary hypertension, aortopulmonary index, pulmonary artery systolic pressure

Date received: 9 February 2021; accepted: 19 February 2021

Introduction
Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease characterized by a pulmonary artery mean pressure (PAMP) that exceeds 25 mmHg. CTEPH is caused by organization of intraluminal thrombi, stenosis and occlusions of the pulmonary artery and its branches, and peripheral vascular remodeling. CTEPH is a chronic complication of acute pulmonary embolism. Obstruction of pulmonary artery branches increases pulmonary vascular resistance (PVR), and this leads to right ventricular overload and right-sided heart failure. The treatment of choice for indicated patients is surgical pulmonary endarterectomy (PEA), which is performed in deep hypothermic cardiac arrest. A total of 25% of patients with CTEPH are diagnosed with residual pulmonary hypertension (RPH) after PEA. RPH is defined by the presence of increased pulmonary artery pressure and PVR 6 months after PEA. RPH is a predictor of an unfavorable outcome after surgical treatment in the early postoperative period during the first year of follow-up and it also increases the risk of periprocedural complications. Prediction of RPH may play a major role in the indication of patients to undergo PEA or to provide them with some additional treatment after PEA.

This study aimed to determine an easy, non-invasive tool to predict RPH after PEA, represented by pulmonary artery systolic pressure (PASP) estimated by echocardiography, by using computed tomography pulmonary angiography (CTPA) images of the pulmonary artery and its branches. Some previous studies described the use of CTPA in association with pulmonary hypertension and even proposed some scoring systems, but none of these systems has been accepted into broader practice yet.

Patients and methods

Study population
This retrospective study included consecutive patients from the Czech Republic who underwent PEA in our center between May 2008 and December 2015. The PEA program started in our center in 2004, and
since then, 393 patients were operated on with an overall 30-day mortality rate of 7.6%. Since 2018, the 30-day mortality rate was 3.8%. The 5-year survival of patients who are operated on in our center is 82.2%. We excluded patients from other countries owing to a lack of detailed follow-up data and patients who died within the first 6 months after surgery because they did not have any required follow-up data. The study was approved by the General University Hospital Ethics Committee (Protocol No. 1141/20 S-IV). Informed consent was not required because of the retrospective nature of the study. All patients were indicated to have a surgical procedure by a multidisciplinary team (pulmonary hypertension specialist, cardiac or thoracic surgeon experienced in PEA, and radiologist) after undergoing a cardiovascular examination with clinical, functional, and hemodynamic assessment. This assessment included echocardiography, a ventilation-perfusion lung scintigraphy scan, right-sided heart catheterization, conventional pulmonary angiography, and CTPA.

**Data sampling**

Clinical and hemodynamic data were collected retrospectively from our database. We collected data on the patients’ age, weight, height, body mass index (BMI), body surface area (BSA), preoperative New York Heart Association (NYHA) functional class, 6-minute walking test (6-MWT) distance, and PASP estimated by echocardiography. Continuous wave Doppler of the tricuspid regurgitation (TR) trace was used to measure the difference in pressure between the right ventricle and right atrium. The simplified Bernoulli equation \( P = 4[TRmax]^2 \) was used to calculate this pressure difference using peak TR velocity. PASP was then calculated by adding the estimated right atrial pressure. Additionally, the following right heart catheterization preoperative data were collected: PASP, PAMP, PVR, and the cardiac index (CI). The follow-up data included PASP estimated by echocardiography, which was recorded at 1, 2, and 3 years after the operation.

A CTPA scan was performed in all patients as a standard examination before PEA. Multidetector computed tomography (CT) scans with multiplanar reconstruction and the volume rendering technique were performed from 2008 to 2012 using the Siemens Somatom Sensation 16 Cardiac CT scanner (Siemens AG, Munich, Germany). CTPA was obtained with the patient in the supine position after intravenous injection of 80 mL of contrast medium (Optiray 350; Guerbet, Princeton, NJ, USA or Iomeron 350, Bracco Imaging Deutschland GmbH, Konstanz, Germany). Contrast medium was administered into the antecubital vein at a rate of 4.0 mL/using a mono-syringe power injector (EnVision CT EDU 700; MedRad, Pittsburg, PA, USA). Scanning was automatically started with a postinjection delay of 6 s by bolus tracking in the main pulmonary artery (PA) with a threshold of 100 HU. One rotation was per 0.5 s. CT scans were obtained with the setting of 100 mAs and 120 kV. CT images were performed using the reconstruction kernel B20f or B30f. From 2012 to 2015, multidetector CT scans were performed on the Philips Brilliance iCT 256 Essential Cardiac CT scanner (Koninklijke Philips Electronics N.V., Amsterdam, The Netherlands). The protocol used was similar to that used in 2008 to 2012 with only a few of the following differences: there was a lower volume of contrast medium applied (50–60 mL), and contrast medium was administered at a rate of 4.0 mL/s, followed by 60 mL of saline
solution at a rate of 5.0 mL/s, using a double-syringe power injector (Stellant; MedRad). The bolus tracking threshold was 130 HU. The tube voltage was 100 kV and the planned tube time-current was 180 mAs. CT images were reconstructed using filter B and the iterative reconstruction technique iDose at level 6.

CT images were analyzed using Dicompass Gateway WebViewer software (Medoro Ltd., Pardubice, Czech Republic) by a single surgeon from our CTEPH team who was trained in CTPA analysis. Images were then reanalyzed in random order by two experienced radiologists, who were blinded to the patients’ clinical and hemodynamic data, but were aware of the patients’ diagnosis of CTEPH. Discrepancies were resolved by consensus.

We measured the diameter of the main pulmonary artery (PA), right pulmonary artery (RPA) and left pulmonary artery (LPA), and the ascending (Ao) and descending (DAO) aorta. We also calculated the following indices using these measurements: Ao/PA, DAO/PA, PA/BSA, PA/BMI, RPA/BSA, RPA/BMI, LPA/BSA, and LPA/BMI.

The diameter of the PA was measured at the level of its bifurcation, perpendicular to its long axis, on an axial slice. The diameter of the Ao was also measured at the level of the bifurcation of the pulmonary trunk (Figure 1) and the diameter of the DAO was measured at the diaphragmatic hiatus (Figure 2A). RPA and LPA diameters were measured at their widest part after bifurcation of the pulmonary trunk (Figure 2B and 2C respectively).

Data analysis
We analyzed the relationships between the diameters of the PA, RPA, and LPA or their indices (indexed to the diameter of the Ao and DAO, BMI, and BSA) and RPH characterized by PASP. We analyzed the postoperative data of patients at 1, 2, and 3 years after the operation.

RPH was defined by a value of PASP > 35 mmHg as estimated by echocardiography. We divided patients into four groups on the basis of their RPH depending on postoperative PASP estimated by echocardiography (group 0 [G0]: no hypertension, G1: mild hypertension, G2: moderate hypertension, and G4: severe hypertension) (Table 1). We then used the Cox regression model to compare the effect of CT measurements/indices on pulmonary hypertension. We attempted to evaluate whether we could predict any residual hypertension (PASP > 35 mmHg) by comparing G0 with G1 + G2 + G3. We also wished to determine whether we could predict moderate and severe hypertension (PASP > 45 mmHg) by comparing G1 + G2 with G2 + G3, and whether we could predict severe hypertension only (PASP > 60 mmHg) by comparing G0 + G1 + G2 with G3.

Because the Ao/PA and DAO/PA indices appeared to be significant in several of the tests, we decided to set cut off values for risk stratification regarding RPH. The cut off values were set by the distribution of data (lower quartile, median, and upper quartile). We analyzed the distribution of patients with and without RPH 1 year after PEA within these intervals. We used the chi-square test to analyze the distribution of cut off values.

Statistical methods
All statistical analyses were performed using STATISTICA 12 software (StatSoft CR Ltd., Prague, Czech Republic). Two-tailed p values of <0.05 were considered statistically significant. Summary statistics (mean ± standard deviation) were calculated. The Cox regression model of proportional risks for investigating the effect of several variables on the
time a specified event takes to occur was used to analyze the effect CT measurements/indices on postoperative PASP. Scatter plot graphs were used to evaluate the relationships between the Ao/PA and DAo/PA indices and the difference between preoperative and postoperative PASP.

Figure 1. Computed tomography images showing measurement of the diameters of the main pulmonary artery and ascending aorta.

Figure 2. Computed tomography images showing measurement of the a) descending aorta diameter, b) right pulmonary artery diameter, and c) left pulmonary artery diameter.
Results

Patient characteristics

The study included 78 men and 53 women, with a mean age of 61 ± 11 years (range: 29–80 years). Details of the patient characteristics are shown in Table 2. CT measurements are shown in Table 3.

The postoperative hemodynamic characteristics at 1, 2, and 3 years after PEA are shown in Table 4. The mean NYHA functional class was 15 ± 0.5 at 1 and 2 years after PEA and 1.6 ± 0.6 3 years after PEA. The mean 6-MWT distance is also shown in Table 4.

PASP analysis

There was a significant relationship between the Ao/PA index and postoperative PASP. Therefore, we were able to predict the presence of any RPH (PASP > 35 mmHg) 1 year after the operation (p = 0.033), the presence of moderate and severe hypertension (PASP > 45 mmHg) 1 year after the operation (p = 0.032), and severe hypertension (PASP > 60 mmHg) 2 years after the operation (p = 0.033). There was also a significant relationship between the DAo/PA index and postoperative PASP, where we could predict any RPH 1 year after the operation (p = 0.010), moderate and severe hypertension 1 year after the operation (p = 0.044), and any RPH (p = 0.025) and severe hypertension (p = 0.026) 2 years after the operation. Furthermore, the PA/BMI index showed a significant predictive
value of moderate or severe hypertension 2 years after the operation (p = 0.021, Table 5).

We did not aim to evaluate the presence or degree of RPH only, but also wished to determine the effect of the operation on a reduction in PASP, regardless of its exact value. We used scatter plot graphs to evaluate the relationships between the Ao/PA and DAo/PA indices (which were significant in the previous evaluation) and the difference between preoperative and postoperative PASP estimated by echocardiography. There were significant negative correlations between the difference in PASP before and after the operation and the Ao/PA index (p < 0.001, Figure 3) and with the DAo/PA index (p < 0.001, Figure 4).

### Table 4. Postoperative hemodynamic and clinical characteristics

|                     | One year after PEA | Two years after PEA | Three years after PEA |
|---------------------|--------------------|---------------------|----------------------|
| PASP ≤ 35 mmHg      | 54 (48)            | 49 (54)             | 41 (64)              |
| PASP 36–45 mmHg     | 25 (22)            | 20 (22)             | 10 (16)              |
| PASP 46–60 mmHg     | 19 (17)            | 9 (10)              | 8 (12)               |
| PASP > 60 mmHg      | 15 (13)            | 12 (13)             | 5 (8)                |
| NYHA functional class | 1.5 ± 0.5          | 1.5 ± 0.6           | 1.6 ± 0.6            |
| 6-MWT (m)           | 483 ± 100          | 478 ± 139           | 481 ± 96             |

Data are mean ± standard deviation or n (%).

PEA, pulmonary endarterectomy; PASP, pulmonary artery systolic pressure; NYHA, New York Heart Association; 6-MWT, 6 minute walking test.

### Table 5. Prediction of PASP at 1, 2, and 3 years after the operation

|                     | One year | Two years | Three years |
|---------------------|----------|-----------|-------------|
|                     | >35 mmHg | >45 mmHg | >60 mmHg |
| PA                  | 0.199    | 0.216    | 0.443      |
| Ao/PA               | 0.033    | 0.032    | 0.210      |
| DAo/PA              | 0.010    | 0.044    | 0.330      |
| PA/BSA              | 0.312    | 0.495    | 0.638      |
| PA/BMI              | 0.981    | 0.577    | 0.335      |

Data are shown as p values.

PASP, pulmonary artery systolic pressure; PA, main pulmonary artery; Ao, ascending aorta; DAo, descending aorta; BSA, body surface area; BMI, body mass index.

### Aortopulmonary index analysis

The cut off values of the Ao/PA and DAo/PA indices were set by the distribution of data (lower quartile, median, and upper quartile). The chi-square test showed a significant distribution of the cut off values of the Ao/PA index (p = 0.0098), but not for the DAo/Pa.

The lower quartile values of the aortopulmonary index (≤0.88 for the Ao and ≤0.64 for the DAo) were related to a lower PASP after PEA (72.3% for Ao/PA and 68.3% for DAo/PA as shown by no RPH 1 year after the operation) (Table 6).

### Discussion

PEA is the method of choice for treating CTEPH because it is the only curative
Figure 3. Relationship between the aortopulmonary index (Ao/PA) and the difference in PASP preoperatively and postoperatively. \( p < 0.001 \)
PASP, pulmonary artery systolic pressure; Ao, ascending aorta; PA, main pulmonary artery.

Figure 4. Relationship between the aortopulmonary index (DAo/PA) and the difference in PASP preoperatively and postoperatively. \( p < 0.001 \)
PASP, pulmonary artery systolic pressure; DAo, descending aorta, PA, main pulmonary artery.
option for operable patients that provides improvement in survival, symptoms, and hemodynamic parameters. Prediction of surgical success in the individual patient is still challenging. There are some methods that can be used to predict RPH, but they are either invasive (right-sided heart catheterization and analysis of pulmonary artery pressure and pulmonary capillary wedge pressure curves, and vasodilatation testing) or are not sufficiently accurate (e.g., echocardiography). Several studies focused on prediction of hemodynamic improvement after PEA using non-invasive imaging. Schölzel et al. analyzed data of 52 patients with CTEPH and found that the preoperative PA diameter indexed for BSA was the only independent predictor for hemodynamic improvement after PEA. Heinrich et al. reported that the diameter of the PA and the ratio of the PA and the diameter of the Ao were correlated with preoperative PAMP. Postoperative PVR was negatively correlated with the presence and extent of central thrombi and dilated bronchial arteries observed on preoperative CT scans. Leone et al. performed detailed radiological evaluation of 145 patients with CTEPH. These authors proposed a new CT score, which included distribution of disease, diameter of the PA, the presence of mosaic perfusion, and the degree of tricuspid regurgitation.

We analyzed data of patients in our center to evaluate the possibility of using a non-invasive imaging method to predict the outcome of patients after PEA. Our study showed that CTPA was useful for not only in preoperative anatomical description of the pulmonary arteries, but also in providing a predictive value for RPH after PEA.

As an outcome parameter, we chose PASP estimated by echocardiography because this is monitored once a year during the follow-up period for all patients in our center. With an increasing time after PEA, there was a higher incidence of missing follow-up data and this is why we chose a 3-year follow-up. The most complete follow-up data were in the first year after PEA. This might be one reason for fewer significant results being obtained in the second and third years.

This study has some limitations. Incomplete follow-up data was one of the main limitations of this study (PASP was recorded in 86% of patients 1 year after PEA, in 69% of patients 2 years after PEA, and in 48% of patients 3 years after PEA). Further limitations are the retrospective nature of the study, the limited number of patients, and the monocentric form of this research.

| Table 6. Aortopulmonary index (Ao/PA and DAo/PA) cut off values | Without residual hypertension n (%) | With residual hypertension n (%) |
|---------------------------------------------------------------|-----------------------------------|---------------------------------|
| **Ao/PA interval (p = 0.0098)**                                 |                                   |                                 |
| Ao/PA ≤ 0.88                                                   | 34 (72.3)                         | 13 (27.7)                       |
| Ao/PA > 0.88 and ≤ 1.03                                        | 26 (43.3)                         | 34 (56.3)                       |
| Ao/PA > 1.03                                                   | 12 (50)                           | 12 (50)                         |
| **DAo/PA interval (p = 0.08)**                                 |                                   |                                 |
| DAo/PA ≤ 0.64                                                  | 28 (68.3)                         | 13 (31.7)                       |
| DAo/PA > 0.64 and ≤ 0.82                                       | 34 (51.5)                         | 32 (48.5)                       |
| DAo/PA > 0.82                                                  | 10 (41.7)                         | 14 (58.3)                       |

Ao, ascending aorta; PA, main pulmonary artery; DAo, descending aorta.
The aortopulmonary index, including the Ao/PA and DAo/PA, appears to be the best predictor of outcome after PEA. Although there has been considerable improvement in understanding of the natural history of CTEPH post-PEA, the clinical relevance of RPH remains unclear. This lack of clarity is why we chose to use the Cox regression model to test for three different degrees of hypertension (>35 mmHg, >45 mmHg, and >60 mmHg). The aorto-pulmonary index showed a significant predictive value not only for RPH, but also for a decrease in PASP, regardless of the absolute value. This finding is important for the assessment of surgical success in patients who have an extremely high or low PASP before PEA. This is because the degree of residual hypertension after PEA does not provide an adequate answer to whether the procedure was successful in these patients, and therefore, whether the indication for their operation was appropriate (mild residual hypertension is a perfect result for a patient who has a preoperative PASP of 120 mmHg, but questionable for a patient who has a PASP of 45 mmHg).

In our study, lower quartile values of the aortopulmonary index corresponded to a lower PASP after PEA. This finding suggests that patients with dilatation of the PA before PEA have a better outcome after the operation. Dilatation of the PA is generally considered as a risk factor for patients with pulmonary hypertension. However, this is mainly an issue in patients with primary pulmonary hypertension and inoperable CTEPH, where the risk is associated with compression of the left main coronary artery, or rupture or dissection of the PA with cardiac tamponade. One of the explanations for a better result of PEA in patients with dilatation of PA is as follows. Dilatation of the PA might be associated with more proximal disease due to organization of thrombotic materials in the central part of the pulmonary artery.

However, patients with more peripheral disease, who typically have a poorer outcome, do not develop such dilatation. This possibility requires further research and we are already investigating the relationship of histological characteristics of pulmonary thromboendarterectomy specimens with dilatation of the PA.

Despite the promising role of the aortopulmonary index as a predictor of outcome after PEA, we are aware that this is only one factor in a complex situation in patients with CTEPH. We would like to emphasize that all characteristics and results of patients with CTEPH should be considered and that all patients should be evaluated by surgeons and teams with expertise in PEA.

RPH remains a challenge for those who treat patients with CTEPH. With the promising results of specific medical therapy for patients with CTEPH, efforts for predicting RPH are no longer focused only on the appropriate indication for PEA, but also to properly identify patients who might require some additional therapy after PEA and to follow these patients closely. Apart from specific pharmacotherapy, balloon pulmonary angioplasty and the developing method of pulmonary denervation are also methods for treating RPH. Despite these methods of RPH treatment, its prediction will remain important because of the association of RPH with the risk of periprocedural complications.

**Conclusion**

Preoperative CTPA parameters can be used to assess hemodynamic improvement after PEA. The aortopulmonary index has significant predictive value for RPH and for a reduction in PASP after PEA. Lower values of an aortopulmonary index (≤0.88 for the Ao and ≤0.64 for the DAo) appear to predict a better outcome after PEA.
Acknowledgements

We thank Dr. Patrik Matras from the Department of Radiology, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic, for his advice regarding CTPA analysis and for CTPA measurements.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the General University in Prague and by a Charles University Grant for students (SVV-2020-260-518). No commercial support was provided.

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