Larger pulmonary artery to ascending aorta ratios are associated with decreased survival of patients undergoing pulmonary endarterectomy

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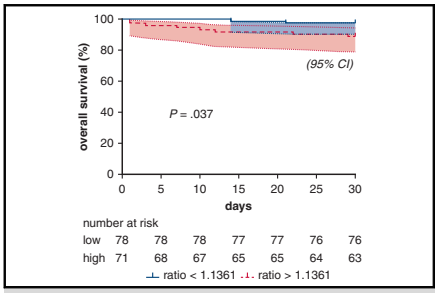
ABSTRACT

Objectives: The ratio of pulmonary artery (PA) and ascending aorta (AA) diameters has recently been shown to be a useful indicator for disease severity and predictor of outcome in patients with pulmonary hypertension and heart failure. This study aimed at evaluating the applicability of this ratio for perioperative risk assessment of patients with chronic thromboembolic pulmonary hypertension undergoing pulmonary endarterectomy.

Methods: In this retrospective cohort study on 149 patients undergoing pulmonary endarterectomy between 2013 and 2020, the preoperative PA to AA ratio was analyzed on axial computed tomography. Variables of pulmonary hemodynamic status were assessed during preoperative right heart catheterization and postoperative Swan-Ganz catheter measurements. Perioperative survival was analyzed by Kaplan-Meier method and log-rank tests.

Results: Preoperative computed tomography measurements showed a median AA diameter of 31 mm (range, 19-47 mm), and a median PA diameter of 36 mm (range, 25-55 mm). The calculated median PA to AA ratio was 1.13 (range, 0.79-1.80). PA to AA ratio correlated positively with PA pressure (systolic, $r = 0.352$ [$P < .001$]; diastolic, $r = 0.406$ [$P < .001$]; mean, $r = 0.318$ [$P < .001$]) and inversely with age ($r = -0.484$ [$P < .001$]). Univariable Cox regression analysis identified PA diameter ($P = .008$) as a preoperative parameter predictive of survival. There was a significant difference (log-rank $P = .037$) in 30-day survival probability for patients with lower PA to AA ratios (<1.136; survival probability, 97.4%) compared with patients with higher ratios (>1.136; survival probability, 88.9%).

Conclusions: PA to AA ratio shows a correlation with other variables associated with pulmonary hypertension. In addition, patients with higher PA to AA ratios have lower survival probabilities after PEA. Further analysis of PA to AA ratio on the selection of chronic thromboembolic pulmonary hypertension for different treatment modalities—pulmonary endarterectomy, medical therapy, and or balloon pulmonary angioplasty—is warranted. (JTCVS Open 2022;10:62-72)



Larger preoperative PA to AA ratios are associated with decreased survival of CTEPH patients undergoing PEA.

CENTRAL MESSAGE

Pulmonary artery to ascending aorta ratio and pulmonary artery diameter can predict perioperative survival and therefore add a brick in the wall of risk assessment for pulmonary endarterectomy.

PERSPECTIVE

Assessment of operability of patients with CTEPH is an interdisciplinary challenge. This study suggests that preoperative PA to AA ratios larger than 1.136 can predict perioperative survival after pulmonary endarterectomy. Routine measurements of PA to AA ratio in preoperative radiological images should thus be encouraged during evaluation and risk assessment for surgery.

See Commentary on page 73.

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Abbreviations And Acronyms

AA = ascending aorta
BPA = balloon angioplasty
CT = computed tomography
CTE = chronic thromboembolic material
CTEPH = chronic thromboembolic pulmonary hypertension
dPAP = diastolic pulmonary artery pressure
DVT = deep venous thrombosis
mPAP = mean pulmonary artery pressure
RA = right atrium
PA = pulmonary artery
PAP = pulmonary artery pressure
PE = pulmonary embolism
PEA = pulmonary endarterectomy
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
sPAP = systolic pulmonary artery pressure
WHO = World Health Organization
WU = Wood Units

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by residual chronic thromboembolic material (CTE) in the pulmonary arteries (PA) resulting in vascular remodeling, pulmonary hypertension, and increased right ventricular afterload.[1] In the majority of cases, the etiology of CTEPH is unclear, but associations with previous deep vein thrombosis or pulmonary embolism,[2] and antiphospholipid syndrome have emerged.[3] Patients primarily present with dyspnea on exertion, and in more advanced stages with dyspnea at rest.[4] Diagnosis is based on the results of right heart catheterization (mean PA pressure [mPAP] $\geq$25 mm Hg and pulmonary artery wedge pressure $\leq$15 mm Hg at rest) and typical vascular lesions, after therapeutic anticoagulation for at least 3 months.[5] Treatment strategies include medical therapy with riociguat, interventional treatment with balloon pulmonary angioplasty (BPA) and surgical pulmonary endarterectomy (PEA). PEA is the gold standard of CTEPH treatment and remains the only curative approach.[2] According to the most recent guidelines, PEA is recommended for all CTEPH patients without contraindications for surgery.[5] In case of inoperability or an unfavorable risk-benefit ratio medical treatment with riociguat—a stimulator of the soluble guanylate cyclase—should be established, potentially leading to a temporary clinical stabilization of the disease.[6] BPA is considered for patients with inoperable CTEPH and persistent or recurrent pulmonary hypertension (PH) after PEA, with limited response or in addition to medical treatment.[5,7,8]

It has recently been discussed that the ratio of PA to ascending aorta (AA) diameters (PA:AA) as measured by cardiac magnetic resonance tomography can predict cardiovascular outcome.[9] Similar results were found for survival in patients with heart failure with preserved ejection fraction.[10] A recent study also suggested a correlation of PA diameter and pulmonary hypertension (PH) diagnosed by transthoracic echocardiography.[11]

The preoperative assessment of perioperative risk and operability of CTEPH patients planned for PEA still lacks strict objective definitions. However, certain preoperative characteristics are associated with favorable surgical outcomes: history of deep venous thrombosis (DVT) or pulmonary embolism (PE), no signs of right heart failure, no comorbidities, functional class II or III, clear disease concordant on all imaging modalities, bilateral lower lobe disease, pulmonary vascular resistance (PVR) < 1000 dyn/sec/cm^{-5}, and higher PA pulse pressure.[8,12,13]

The overall aim of this study was to evaluate the usefulness of PA:AA and PA diameter for perioperative risk assessment in CTEPH patients undergoing PEA. The primary objective was to test the predictive value of preoperative PA:AA and PA diameter determined by computed tomography (CT) for perioperative survival. Secondary study end points included correlations between PA:AA or PA diameter with PH-specific and characteristic perioperative parameters.

MATERIALS AND METHODS

Study Design

This was a retrospective, single-center analysis of all patients undergoing PEA for CTEPH at Medical University of Vienna between January 2013 and April 2020. The study was approved by the review board on human research of the Ethics Committee of the Medical University of Vienna, Austria (EK 1198/2019) on December 12, 2019. Due to the retrospective character of the study, informed consent was not required.

Demographic Data

During the observation period 149 patients with CTEPH underwent PEA at our department. Inclusion criteria were the availability of preoperative CT of the thorax and preoperative right heart catheterization. Patients undergoing PEA for acute pulmonary embolism, PA intimal sarcoma, or hydatid disease were excluded.

Preoperative Workup of CTEPH Patients

Patients routinely underwent echocardiography, right heart catheterization, and pulmonary angiography at the Division of Cardiology before surgery. Measured variables included diameters of heart cavities, inferior vena cava, and intraventricular septum, tricuspid annular plane systolic excursion, pulmonary velocity acceleration time, and tissue Doppler imaging of the right ventricle. Further variables that were evaluated were PA pressure during systole (sPAP), diastole (dPAP), and mean pressure (mPAP). Moreover, PVR, calculated with Fick method in Wood units and cardiac index were measured. Cardiac output was measured and calculated by indirect Fick method.[14]

CT

Image data were acquired on 2 different dual-source CT systems (Somatom Definition Flash and Somatom Force, Siemens Healthineers). A

nonionic contrast agent (Imeron 400; Bracco) with a weight adapted dose was injected at a flow rate of 4 mL/sec through a peripheral vein of the forearm or central line. On both scanners, the scan was triggered using bolus tracking, with a threshold of 100 Hounsfield units above the baseline measurement at the pulmonary trunk. Scans were acquired in caudo-cranial direction. Patients were instructed to breath-hold in inspiration during scan acquisition. Anatomical tube current modulation (CARE Dose 4D; Siemens Healthineers) was applied per default in all patients. In addition, automated tube potential control (CARE kV; Siemens Healthineers) was applied. Iterative reconstruction was applied to all image reconstructions using either SAFIRE (second-generation Dual Source Dual Energy Somatom Definition Flash) or ADMIRE (third-generation Dual Source Dual Energy Somatom Force) algorithms. Images were reconstructed at a slice thickness of 1 mm with a position increment of 1 mm using a medium soft kernel.

CT scans were performed within 30 days of surgery. Measurements were performed in the mediastinal window in an axial view at the level of the pulmonary trunk. Short axes diameters of PA were measured at the widest part of PA before the bifurcation, AA diameters were subsequently measured at the same level, and both reported in mm. An example is shown in Figure 1.

PEA Technique and Classification of CTE Material

In the operating room, patients received standard monitoring, including cerebral oximetry, PA catheter (Swan-Ganz catheter), and transesophageal echocardiography. Patients were brought in supine position and surgery was routinely performed via sternotomy. Cardiopulmonary bypass with bicaval venous cannulation and arterial cannulation in the AA was employed. Vent cannulas were placed in the left atrium and the pulmonary trunk, and a catheter for antegrade cardioplegia was inserted. Bilateral sequential PEA was performed in deep hypothermia (18° C) and brief periods of circulatory arrest.[15] To continuously monitor postoperative left atrial pressures, a 5Fr polyethylene catheter was inserted via the Sondegard groove.

Surgical specimens were categorized with The University of California, San Diego, Surgical classification,[15] classifying the disease into levels according to the anatomical extent of CTE: Level 0-no CTE; Level I-CTE at the level of the main PA; Level IC-complete occlusion and nonperfusion of 1 lung; Level II-CTE at level of lobar or intermediate arteries; Level III-CTE at segmental level; and Level IV-CTE at subsegmental level.

Postoperative Management

After surgery patients were routinely transferred to the intensive care unit for further observation. PA catheters were left in situ and used for measurements of PAP, PVR and cardiac index within the first 3 postoperative days. Anticoagulation was continued with low molecular weight heparin with 0.5 mg/kg body weight, twice per day, subcutaneously. Long-term follow-up examinations were performed in the respective referral centers.

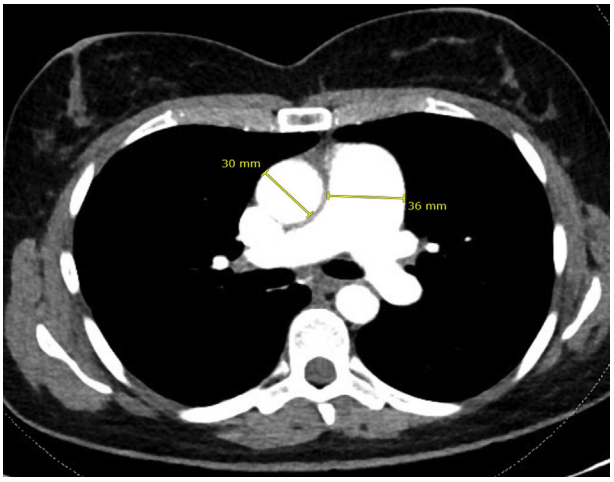

FIGURE 1. Example of measurement of the vessels in an axial computed tomography (CT) scan at the level of the pulmonary trunk.

Statistical Methods

Statistical analysis of data was performed using SPSS software version 25.0 (IBM-SPSS Inc). GraphPad Prism version 6.00 for Windows (GraphPad Software) was used for graphical display of all Kaplan-Meier curves and scatterplots in this work.

Normality was tested with the help of Shapiro-Wilk test and graphically with histograms. Normally distributed metric data were reported as mean ± SD, median and ranges were used for nonnormal distributions. Categorical data were depicted with absolute and relative frequencies.

Pearson correlation coefficient (r) was calculated to establish associations between PA:AA and other parameters, with 0.1 to 0.4 indicating weak, 0.4 to 0.7 moderate, and 0.7 to 1 strong correlation. Univariable Cox regression analysis was performed to assess the prognostic influence of clinically relevant variables on perioperative outcome. Follow-up included the first 30 days after surgery. Overall perioperative survival was calculated with Kaplan-Meier survival analysis and log-rank tests. Subgroups were divided according to optimal cutoff values, defined by previously calculated Youden indices.

RESULTS

Baseline Characteristics and Comorbidities

The study population comprised 149 patients with 90 (60.4%) men. The median age at the time of surgery was 58 years (range, 22-77 years). Preoperatively, patients were categorized into 4 groups according to World Health Organization (WHO) functional class reflecting the clinical severity of CTEPH, depending on their level of dyspnea and limitation of daily activities. One (0.7%) patient was in group I with no impairment, and 36 (24.2%) patients were in group II with mild impairment of daily activities. The majority of 93 (62.4%) patients were in WHO functional class III, indicating significant limitations in daily life activities, and 19 (12.8%) patients had symptoms at rest (group IV).

In terms of comorbidities, 20 (13.4%) patients experienced coronary artery disease, none of whom had undergone coronary artery bypass graft surgery. Two patients had had valve replacement surgery (biological tricuspid valve) due to previous endocarditis. There were also 2 cases of advanced chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease III and IV, respectively). A total of 12 (8.1%) patients experienced chronic kidney disease and 44 (29.5%) had systemic arterial hypertension. Thirty-nine (26.2%) patients had no history of DVT and/or PE. Eleven (7.4%) patients had had at least 1 episode of prior DVT, 54 (36.2%) patients had experienced at least 1 occurrence of PE, and 45 (30.2%) had had both.

Preoperative Diagnostics

Median vessel diameters at the level of the pulmonary trunk were 36 mm for PA, and 31 mm for AA. Based on these measurements, PA:AA was calculated for each

patient, resulting in an overall median of 1.13. Detailed results of right heart catheterization and CT scan measurements are summarized in Table 1, additional parameters from preoperative echocardiography are depicted in Table E1.

PEA and Perioperative Management

Macroscopic classification of surgical specimens is depicted in Table 2. Combined surgeries were performed in a total of 12 (8.1%) patients, including PEA together with single coronary artery bypass grafting in 4 and double coronary artery bypass graft in 2 patients. Tricuspid valve reconstruction, tricuspid valve replacement, mitral valve replacement, closure of a patent foramen ovale, thymectomy (intraoperative detection of suspicious thymic hyperplasia, histologically thymitis), and pulmonary wedge resection (diagnostics of a single pulmonary nodule in the right upper lobe) were performed in 1 patient each.

Postoperative Course and Complications

Two patients were extubated in the operating room directly after surgery, and were transferred to the intensive care unit without mechanical ventilation. Patients required intensive care for a median of 6 days (range, 1-42 days) before transfer to the normal ward.

Of the 149 patients undergoing PEA, 22 (14.8%) were supported with prolonged venoarterial extracorporeal membrane oxygenation postoperatively. The median duration of postoperative extracorporeal membrane oxygenation was 6 days (range, 1-15 days) for patients who could be weaned successfully.

TABLE 1. Baseline characteristics and preoperative data (N = 149)

Variable	Result
Basic demographic data	
Male sex	90 (60.4)
Age (y)	58 (22-77)
BMI	26.88 (16.61-44.44)
Preoperative right heart catheter	
sPAP (mm Hg)	84 (29-153)
dPAP (mm Hg)	28 (8-79)
mPAP (mm Hg)	47 (17-92)
PVR by Fick method (WU)	8.88 (2.30-21.81)
Cardiac index (L/min/m^2)	2.24 (1.19-6.40)
Preoperative computed tomography	
PA diameter (mm)	36 (25-55)
AA diameter (mm)	31 (19-47)
PA to AA ratio	1.13 (0.79-1.80)
PA diameter/BSA by du Bois method (mm/m^2)	18.08 (12.11-27.50)

Values are presented as n (%) or median (range). *BMI*, Body mass index; *sPAP*, systolic pulmonary artery pressure; *dPAP*, diastolic pulmonary artery pressure; *mPAP*, mean pulmonary artery pressure (in mm Hg), *PVR*, pulmonary vascular resistance; *WU*, Wood Units; *PA*, pulmonary artery; *AA*, ascending aorta; *BSA*, body surface area.

TABLE 2. Peri- and postoperative data (N = 149)

Variable	Result
UCSD classification of surgical specimens	
Level I	19 (12.7)
Level IC	9 (6.0)
Level II	56 (37.6)
Level III	64 (43.0)
Level IV	1 (0.7)
ICU stay (d)	6 (1-42)
Postoperative hospital stay (d)	12 (5-66)
Postoperative ECMO	22 (14.8)
Duration of postoperative ECMO (d)	6 (1-15)
Hemofiltration during hospital stay	10 (6.8)
Length of mechanical ventilation (d)*	2 (0-42)
Reintubation	5 (3.4)
Tracheotomy	12 (8.1)
Postoperative Swan-Ganz catheter measurements†	
sPAP (mm Hg)	42 (23-86)
dPAP (mm Hg)	19 (7-37)
mPAP (mm Hg)	28 (14-55)
PVR (WU)	2.83 (0.84-9.95)
Cardiac index (L/min/m2)	2.90 (1.68-8.03)

Values are presented as n (%) or median (range). *UCSD*, University of California, San Diego; *ICU*, intensive care unit; *ECMO*, extracorporeal membrane oxygenation; *sPAP*, systolic pulmonary artery pressure; *dPAP*, diastolic pulmonary artery pressure; *mPAP*, mean pulmonary artery pressure; *PVR*, pulmonary vascular resistance; *WU*, Wood Units. *Including tracheotomy. †Excluding all patients on postoperative ECMO (n = 22).

Mild or severe postoperative cardiovascular events occurred in 26 (18.3%) patients, mainly atrial fibrillation in 17 (11.4%) cases. Diffuse bleeding, severe sinus tachycardia, and episodes of bradycardia occurred in 2 patients each. One patient was successfully resuscitated after an episode of ventricular fibrillation.

PA:AA Correlates With PAP and Inversely Correlates With Age

Although there was no correlation of PA diameter with age ($r = 0.099$; $P = .229$), there was a moderate correlation of AA diameter with age ($r = 0.600$; $P < .001$) (Figure 2, *A*). Furthermore, there was a moderate negative correlation of PA:AA with age ($r = –0.484$; $P < .001$) (Figure 2, *B*).

There were moderate correlations of PA diameter with sPAP ($r = 0.515$; $P < .001$), dPAP ($r = 0.610$; $P < .001$), and mPAP ($r = 0.578$; $P < .001$) (Figure 2, *C*), and with PVR ($r = 0.236$; $P = .004$) and cardiac index ($r = –0.185$; $P = .026$), respectively. Also, there were weak positive correlations between PA:AA and sPAP ($r = 0.352$; $P < .001$), dPAP ($r = 0.406$; $P < .001$), and mPAP ($r = 0.318$; $P < .001$), as well as with PVR ($r = 0.163$; $P = .050$), depicted in Figure 2, *D*. There was no significant correlation between PA:AA and cardiac index ($P = .451$),

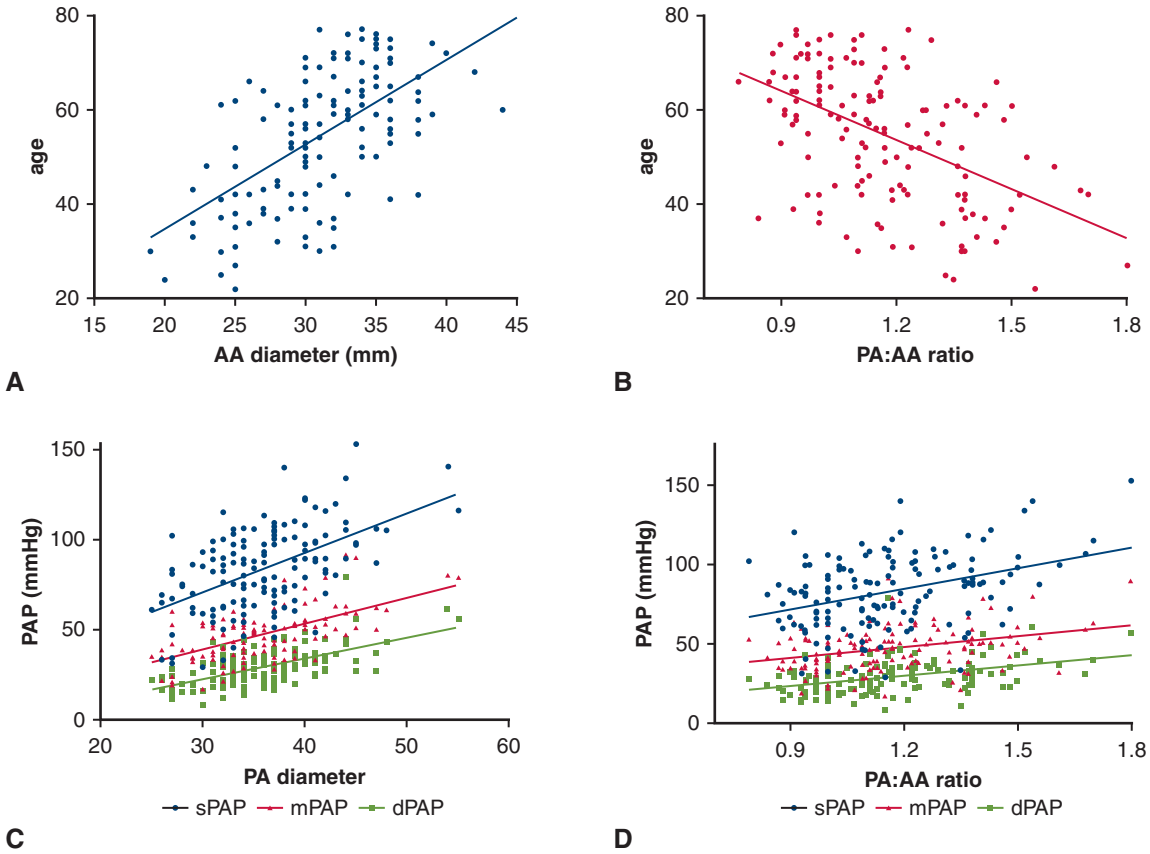

FIGURE 2. Correlation of pulmonary artery (*PA*) and ascending aorta (*AA*) diameters with age and pulmonary artery pressure (*PAP*). A, Positive correlation between AA diameter and age. B, Negative correlation between PA to AA ratio and age. C, positive correlations between PA diameter and preoperative PAPs (systolic [sPAP], mean [mPAP], and diastolic [dPAP]). D, Positive correlations between PA to AA ratio and preoperative PAPs (sPAP, mPAP, and dPAP).

preoperative WHO functional class ($P = .117$), or surgical specimen classification ($P = .328$).

Results of Uni- and Multivariable Analysis

At univariable analysis, 3 parameters were significant prognostic factors for perioperative survival: preoperative PA diameter ($P = .008$) and right atrial diameter ($P = .001$), as well as preoperative dPAP ($P = .047$). Parameters with $P < .05$ were included in the multivariable model (Table 3).

Mortality

Ten (6.7%) patients died within the 30-day follow-up period after surgery (for details see Appendix 1). The institutional perioperative mortality during the study period was 5%. The higher perioperative mortality of the current study with 6.7% is explained by study inclusion and exclusion criteria (see Methods).

Higher PA:AA Predict Lower Survival Probabilities

The Youden index revealed an optimal cutoff value of 1.1361 for PA:AA ($J = 0.35$; sensitivity, 80%; specificity, 55%). Thirty-day survival probabilities were 97.4% for patients with lower PA:AA < 1.136 (95% CI, 93.9%-100.0%) and 88.9% for patients with higher ratios >1.136 (95% CI, 81.6%-96.2%), respectively. There was a significant survival benefit for patients with preoperatively lower PA:AA than in those with higher ratios (log-rank $P = .037$) (Figures 3, *A*, and 4).

In terms of PA diameter, the Youden index showed an optimal cutoff value of 37.5 mm ($J = 0.51$; sensitivity, 80%; specificity, 71%) predicting survival. There was a highly significant difference (log-rank $P = .001$) (Figure 3, *B*) between patients with smaller PA diameters (≤37 mm; survival probability, 98.0%; 95% CI, 95.3%-100.0%) compared with the patient group with larger diameters (≥38 mm; survival probability, 83.3%, 95% CI, 72.7%-93.9%). For all 95% CIs, see Table 4.

DISCUSSION

Operability and Risk Assessment

PEA is potentially curative surgery for CTEPH. Careful operability assessment must ensure that CTEPH patients with operable disease are not misclassified as inoperable

TABLE 3. Univariable and multivariable analyses

Analysis	Hazard ratio	95% CI	*P* value
Univariable			
Male sex	1.545	0.400-5.975	.528
Age	1.015	0.969-1.064	.525
Prior diagnosed DVT (no)	2.435	0.517-11.465	.260
Prior diagnosed PE (no)	2.065	0.598-7.134	.252
Arterial hypertension (yes)	1.674	0.472-5.932	.425
CAD (yes)	1.634	0.347-7.694	.535
WHO FC (III or IV vs I or II)	31.952	0.076-high*	.261
PA diameter	1.131	1.033-1.237	**.008**†
AA diameter	1.098	0.966-1.247	.152
PA to AA ratio	3.693	0.185-73.886	.393
RA diameter	1.101	1.041-1.166	**.001**†
RV diameter	1.041	0.967-1.121	.289
LV-RV ratio	0.233	0.011-5.055	.353
Pre sPAP	1.015	0.989-1.043	.256
Pre dPAP	1.044	1.001-1.088	**.047**†
Pre mPAP	1.032	0.991-1.075	.128
Pre PVR	1.066	0.924-1.228	.381
Pre cardiac index	0.739	0.259-2.108	.572
Multivariable			
PA diameter	1.068	0.890-1.281	.479
RA diameter	1.089	1.020-1.162	**.011**†
Pre dPAP	0.990	0.896-1.094	.845

DVT, Deep vein thrombosis; *PE*, pulmonary embolism, *CAD*, coronary artery disease, *WHO*, World Health Organization; *FC*, functional class; *PA*, pulmonary artery; *AA*, ascending aorta; *RA*, right atrium; *RV*, right ventricle; *LV*, left ventricle; *sPAP*, systolic pulmonary artery pressure; *dPAP*, diastolic pulmonary artery pressure; *mPAP*, mean pulmonary artery pressure; *PVR*, pulmonary vascular resistance. *Value of 100 or more. †Boldface type indicating statistical significance.

and potentially curative PEA is denied. Risk assessment includes evaluation of comorbidities and hemodynamic status. The assessment of operability still harbors a subjective element for many cases; thus, the recommendation to refer suspected CTEPH patients to an expert center for confirmation of diagnosis and treatment is an important message of the guidelines.[8,13]

Current surgical classification systems distinguish four levels of CTEPH according to the most proximal anatomical extent of chronic thromboembolic material.[15,16] Because the surgical specimen is required for classification, this can only be applied intraoperatively, but not for operability assessment before PEA. Recently, a preoperative classification system incorporating the PA occlusion technique, to detect the presence of small vessel disease that may be more amenable to medical therapy, has been proposed.[17] In this pre-PEA classification system, class C patients, defined as having a ventilation/perfusion scan supportive of CTE disease, PVR >1100 dyn/sec/cm^{-5}, upstream resistance <60%, carry a higher risk for persistent PH and death after PEA. Decreased upstream resistance, determined by PA occlusion waveform analysis was an independent predictor of persistent PH and survival.[18]

PA:AA as a Useful Outcome Predictor After PEA

Several previous studies have focused on the feasibility of using vessel diameters from noninvasive radiologic examinations, such as CT or magnetic resonance imaging scans, for the diagnosis of PH in unselected cardiac patients[19,20] or those with underlying heart failure with preserved ejection fraction.[10] Kammerlander and colleagues[9] suggested that a higher PA:AA was predictive for unfavorable outcome in cardiac patients with higher rates of heart failure, myocardial infarction, and stroke. Moreover, 2 studies found increased rates of transplantation and death in patients with interstitial lung disease and higher PA:AA.[21,22]

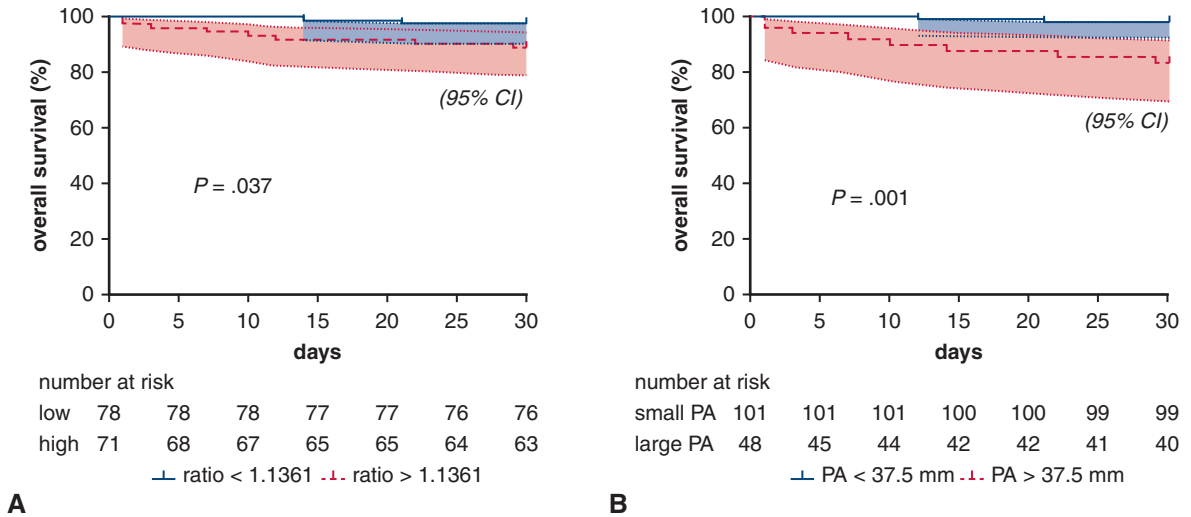

FIGURE 3. Survival outcomes. Perioperative survival (30 days) compared between (A) higher and lower pulmonary artery (*PA*) to ascending aorta (AA) ratios, and (B) larger and smaller PA diameters. For 95% CIs see Table 4.

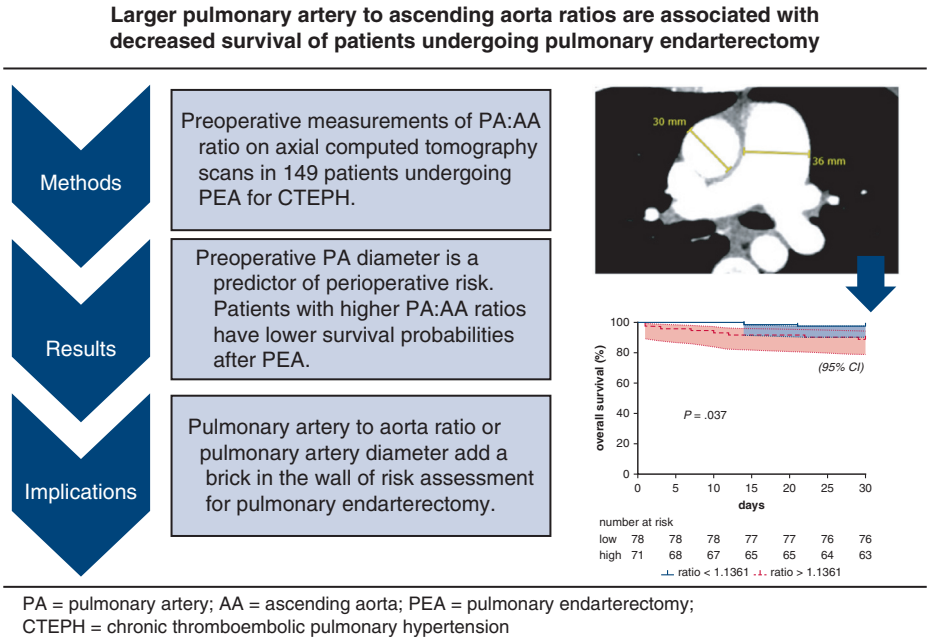

FIGURE 4. An overview of methods, results, and clinical implications of the study. Example of measurement of the vessels in an axial computed tomography (CT) scan at the level of the pulmonary trunk (*right upper*), perioperative survival (30 days) compared between higher and lower PA to AA ratios (*right lower*). For 95% CIs, see Table 4. *PA*, Pulmonary artery; *AA*, ascending aorta; *PEA*, pulmonary endarterectomy; *CTEPH*, chronic thromboembolic pulmonary hypertension.

The present study aimed to determine the relevance of PA:AA for the perioperative risk assessment in patients with advanced CTEPH undergoing PEA. Our study included a large cohort of patients with confirmed CTEPH scheduled for PEA. Median PA:AA was 1.13 in our study, which is considerably higher than the reference value of 0.9 for healthy adults as described by Truong and colleagues.[23] In our collective, a higher PA:AA >1.136 was associated with significantly higher perioperative mortality after PEA. Addition of PA:AA for selection of CTEPH for PEA instead of medical therapy and or BPA may add further improvement to good PEA outcomes.

CTEPH patients undergoing PEA are a very rare and specific patient collective. In comparison to cardiologic patient collectives in the existing literature on the subject, the patients in our study were considerably younger and experienced a more severe form of CTEPH with noticeable restrictions in their daily activities. The severity of the disease is reflected by the results from preoperative right heart catheterization with a median PAP of 47 mm Hg, compared with average values ranging from 23 to 46 mm Hg in other studies, also including patients with only mild PH.[10,20] We found correlations of PA:AA with PH-specific measurements and calculations pertaining to disease severity: sPAP, dPAP, and mPAP, and PVR, but not with more subjective characteristics such as WHO functional class. Overall, these results are in line with previous studies, in which the ratio was useful to distinguish between PH versus non-PH patients.[10,19]

TABLE 4. 95% CI of survival probabilities for pulmonary artery to ascending artery ratio (PA:AA) and PA diameter (Figure 3, *A* and *B*)

Probability	95% CI*						
PA:AA							
Days	0	5	10	15	20	25	30
Low	0.96-1.0	0.96-1.0	0.96-1.0	0.96-1.0	0.96-1.0	0.94-1.0	0.94-1.0
High	0.93-1.0	0.91-1.0	0.89-1.0	0.85-0.98	0.85-0.98	0.83-0.97	0.81-0.96
PA diameter							
Days	0	5	10	15	20	25	30
Small	0.97-1.0	0.97-1.0	0.97-1.0	0.97-1.0	0.97-1.0	0.95-1.0	0.95-1.0
Large	0.90-1.0	0.87-1.0	0.84-1.0	0.79-0.94	0.79-0.94	0.75-0.95	0.73-0.94

PA, Pulmonary artery; *AA*, ascending aorta. *95% CIs of perioperative Kaplan-Meier survival probabilities comparing lower and higher PA:AA ratios (Figure 3, *A*), as well as smaller and larger PA diameters (Figure 3, *B*).

Usefulness of PA and AA Diameter

Prior CT studies described PA and AA diameters in healthy adults. The mean AA diameter was reported with 31.1 mm in women and 33.6 mm in men with upper limits of normal of 35.6 mm, 38.3 mm, and 40 mm in women and 37.8 mm, 40.5 mm, and 42.6 mm in men. There was a statistically significant linear association of AA diameter with age, gender, descending aortic diameter, and PA diameter.[24] The mean PA diameter in healthy adults was 24 mm (upper limit of normal, 29.5 mm). PA diameter was reported to correlate with body mass index and patient weight, but not height. PA diameters did not reveal statistically significant gender differences.[25] Although the median AA diameter of 31 mm in our patient collective is in close proximity to the reported standard mean AA diameter of 31.1 mm, the median PA diameter of 36 mm is beyond the upper limit of normal in Bozlar and colleagues.[25]

In a study by Schölzel and colleagues[26] on 52 patients undergoing PEA, PA:AA was not a predictor of improvement or survival. They did identify preoperative indexed PA diameter as the only independent predictor for hemodynamic improvement after PEA, which was defined as PVR <500 dyn/sec/cm^{-5} and a mPAP <35 mm Hg measured 3 days after PEA.[26] Various other studies found correlations between PA diameter and outcome variables in different patient cohorts. The extent of PA dilatation was found to be associated with more severe forms of PH defined by an mPAP >30 mm Hg in patients with heart failure with preserved ejection fraction,[10] as well as a significantly higher rate of unexpected deaths in patients with PAH or CTEPH.[27] Moreover, PA diameters were shown to be significantly larger in patients with severe aortic stenosis and PH compared with those without signs for PH.[28] In terms of outcome after BPA for inoperable CTEPH, larger PA diameters were associated with a higher amount of mild complications postinterventionally.[29]

In our study, PA diameter correlated well with preoperative PH specific measurements such as sPAP, dPAP, and mPAP, and PVR; as well as perioperative PEA survival. Whereas PA diameter did not correlate with patient age, AA diameter increased significantly with age in the CTEPH patient cohort. Moreover, preoperative PA diameter was shown to be a relevant predictor for perioperative outcome after PEA.

The correlation of PA diameter measured on CT sections with PAP and PVR can by no means replace the direct measurements performed in accordance with current guidelines by the European Respiratory Society[8] by right heart catheterization. Nevertheless, the information of PA diameter being an independent prognostic factor for perioperative risk regarding survival following PEA adds another element of perioperative risk assessment for PEA.

In our patient cohort, preoperative AA diameter was not an independent prognostic factor for perioperative survival. This may be the result of a limitation of this study; only patients who underwent PEA were included in the analysis. Patients with larger AA diameters may have been declined during operability assessment.

In addition to the determination of reference values for healthy people, cutoff values have to be adapted for specific applications, as was done in this study for perioperative risk assessment for PEA.

Limitations of the Study and Outlook

The project carries the characteristic weaknesses of orphan disease research.[30] One particular limitation is that only CTEPH patients, who were candidates for surgical resection, were available for this study. Because the study was carried out as a single-center analysis, we were faced with a limited sample size.

Despite these limitations, determining PA:AA during the surgical evaluation process of CTEPH patients might offer additional grounds for patient selection. Incorporation of PA:AA—together with well-established parameters such as PAP and PVR—in patient selection criteria could enhance the decision-making process in interdisciplinary CTEPH boards. Further prospective, multicenter studies are thus necessary to test the validity of PA:AA as outcome predictor after PEA in a larger patient cohort.

CONCLUSIONS

PA:AA shows a correlation with other variables associated with PH. Patients with higher PA:AA have lower perioperative survival probabilities after PEA. A pitfall of the PA:AA may lie in its inverse correlation with age. Further analysis of PA:AA on the selection of CTEPH for different treatment modalities—PEA, medical therapy, and or balloon pulmonary angioplasty—is warranted, as well as prospective studies testing the validity of PA:AA as an outcome predictor.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: pulmonary hypertension, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, computed tomography, PA to AA ratio

APPENDIX 1. MORTALITY

The institutional perioperative mortality during the study period was 5%. The higher perioperative mortality of the current study with 6.7% is explained by study inclusion and exclusion criteria (see Methods).

Three male patients died due to acute massive pulmonary embolism (PE) despite rescue extracorporeal membrane oxygenation (ECMO) implantation after technically successful pulmonary endarterectomy (PEA) of all segments with reduction of postoperative pulmonary artery pressure (PAP) (ie, age [years], preoperative hemodynamic status, and chronic thromboembolic pulmonary hypertension [CTEPH] surgical class): 64a: 63 mm Hg, 11.85 Wood Units (WU), level 1C; 62a: 33 mm Hg, 13.20 WU, level 1, and 61a: 61 mm Hg, 10.36 WU, level 1; on postoperative days (POD) 1, POD3, and POD7, respectively.

Three patients with advanced and high-risk hemodynamic profiles (ie, gender, age [years], preoperative hemodynamics, and CTEPH surgical class) female, 66a: 60 mm Hg, pulmonary vascular resistance (PVR) of 17.78 WU, level 1, diffuse bleeding; male, 75a, 59 mm Hg, 7.63 WU, level 2; and male, 72a, 44 mm Hg, 9.93 WU, level 3 with abundant red clot) died on POD1, POD10, and POD14, respectively; because of persistent pulmonary hypertension after technically successful PEA with prolonged venoarterial ECMO support.

A 32-year-old male patient with a history of PE and severe pulmonary hypertension (mean PAP, 50 mm Hg and PVR, 8.04 WU) considered a borderline candidate for PEA underwent balloon angioplasty to improve his hemodynamic situation before PEA. After 2 balloon angioplasty sessions, there was no clear hemodynamic improvement. Subsequent PEA (removal of level 3 specimens) did not transfer in a significant PAP reduction. Because his hemodynamic situation did not improve on prolonged venoarterial ECMO over several days the patient underwent bilateral lung transplantation. The perioperative period was complicated by severe diffuse bleeding based on extremely poor coagulation parameters. The patient died on POD22 due to multiorgan failure caused by multiple PEs and diffuse bleeding.

A 31-year old man underwent re-PEA for recurrence of CTEPH (mean PAP, 78 mm Hg and PVR, 11.80 WU) 6 years after successful PEA because of inadequate anticoagulation. The patient could not be weaned from prolonged ECMO and deceased due to necrotizing pneumonia on POD29.

A 77-year-old female patient with chronic kidney insufficiency and a history of fasciotomy for spontaneous bleedings under oral anticoagulation with mean PAP of 35 mm Hg and PVR of 6.60 WU underwent successful PEA (level 2 specimen) with resultant normalization of PAP and PVR. She developed acute retroperitoneal hemorrhage 3 weeks after surgery resulting in multiorgan failure (death at POD21).

A multimorbid 35-year-old woman with a history of intravenous drug abuse underwent re-resternotomy for tricuspid valve replacement and concomitant PEA. Pulmonary hypertension was not amenable to PEA and the patient died on POD12 due to right heart failure.

TABLE E1. Preoperative echocardiography (N = 149)

Preoperative echocardiography	Result	Range	Interquartile range
2D LV diameter (mm)	38	21-60	33-43
2D RV diameter (mm)	48	25-74	41-55
2D LA diameter (mm)	55	32-80	49-61
2D RA diameter (mm)	62	43-96	55.5-68.5
IVC diameter (mm)	21	12-43	16.5-25.5
IVS (mm)	11	7-16	10-12
PV-AT (msec)	74	38-134	62-86
TAPSE (mm)	16	7-29	13.5-18.5
TDI-RV (msec)	0.11	0.04-0.21	0.08-0.14
LV-RV ratio	0.76	0.32-1.65	0.58-0.94

2D, Two dimensional; *LV*, left ventricle; *RV*, right ventricle; *LA*, left atrium; *RA*, right atrium; *IVC*, inferior vena cava; *IVS*, intraventricular septum; *PV-AT*, pulmonary velocity acceleration time; *TAPSE*, tricuspid annular plane systolic excursion; *TDI-RV*, tissue Doppler imaging of the RV.