Feasibility of a noninvasive operability assessment in chronic thromboembolic pulmonary hypertension under real-world practice.

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Research

Keywords: Hypertension, Pulmonary, Pulmonary Embolism, Endarterectomy.

Posted Date: March 25th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-19302/v1

Abstract

Background – The development of an optimized assessment of operability in patients with chronic thromboembolic pulmonary hypertension (CTEPH) is crucial. This study aimed to evaluate the feasibility of a noninvasive operability assessment of CTEPH based on multidetector computed tomographic angiography (MCTA).

Methods –176 patients with CTEPH were evaluated from January 2016 to April 2018. Throughout the first phase, operability was assessed with MCTA and pulmonary angiography (PA): initial surgical decision was made based on MCTA with further analysis of PA to evaluate which cases initial decision was not modified by PA. During the second phase, PA was limited to patients judged inoperable based on MCTA or in those whose assessment was not possible.

Results – Patients deemed operable (50%) based on MCTAalong the first phase, had been adequately classified, as PA did not modify the initial decision in all but one patient. Comparable results were obtained throughout the implementation phase, in which decision of operability was based on MCTA in 49% of the patients. Regarding operated patients, decision of operability had been based solely on MCTA in 94% of those with level I disease regarding intraoperative CTEPH classification; in 75% with level II disease and 54% with level III. This approach enabled shorter time periods to complete surgical assessment and the avoidance of PA-related morbidity. Baseline parameters, postoperative measures and survival rates at 1 year after surgerywere comparable in both phases.

Conclusions - Noninvasive operability assessment is feasible in a subset of CTEPH patients and optimizessurgical candidacy evaluation.

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) represents the third most common cause of pulmonary hypertension (PH) [1] and the only form that is potentially curable [2].

The diagnosis of CTEPH requires the demonstration of pulmonary hypertension on right heart catheterization, along with mismatched perfusion defects on ventilation/perfusion (V/Q) scintigraphy and signs of CTEPH in advanced imaging techniques [3, 4].

Once the diagnosis is confirmed, the next pivotal step consists of assessing the suitability for pulmonary endarterectomy (PEA), which offers the best chance of improved long-term outcomes [5, 6].

Operability assessment of patients with CTEPH is complex and accounts for surgical accessibility of the thrombi, concordance between surgically accessible vascular obstruction and pulmonary vascular resistance and evaluation of underlying comorbidities prohibiting PEA [4, 5].

The advanced imaging techniques recommended for the operability assessment of CTEPH include multidetector computed tomographic angiography (MCTA), magnetic resonance (MR) imaging and

conventional pulmonary angiography (PA) [3, 4].

PA is still considered the gold standard for the assessment of pulmonary vasculature. Nevertheless, its routine use is being challenged by advances in noninvasive technology such as the MCTA, which has proven high sensitivity and specificity in detecting thromboembolic disease at lobar and segmental levels [7, 8]. Additionally, although PA is considered a safe technique it is an invasive procedure non-exempt from complications [9, 10].

Recent years have resulted in an increasing CTEPH imaging expertise at our institution alongside the growing healthcare burden as a national CTEPH referral center[11]. We have therefore sought to evaluate the performance of a noninvasive operability assessment in patients with CTEPH as a strategy to optimize surgical candidacy appraisal in relation to the quality of care, efficiency, cost reduction and patient safety.

Methods

Study protocol

As a national CTEPH referral center, patients with presumed CTEPH, either diagnosed at our institution or oftentimes, referred from external hospitals; are assessed at a weekly multidisciplinary team (MDT) meeting.

Upon feasibility analysis of noninvasive operability assessment, the study was divided into two consecutive phases. Along the pilot phase, which was developed from January 2016 to March 2017, every patient was assessed at the MDT meeting with both MCTA and PA: MCTA findings were initially analyzed, ultimately deciding which patient was either 1) suitable for surgery 2) unsuitable for surgery or 3) whose assessment was unattainable (because of suboptimal MCTA imaging or thromboembolic disease at the limit of surgical accessibility for PEA). Once classified in these three groups, PA images were evaluated in order to analyze in which patients the initial decision of operability based on MCTA imaging were unmodified by PA findings (Fig. 1.1).

During the second phase, implemented from April 2017 to April 2018, the non-invasive operability assessment was launched. In this period, MCTA was performed as the only imaging technique prior to the MDT meeting. A complementary PA was only conducted in two patient groups: 1) where assessment was unachievable (due to either suboptimal MCTA imaging or thromboembolic disease at the limit of surgical accessibility); 2) in patients judged inoperable based on MCTA, in order to ensure that no operable patient was misclassified as inoperable and denied PEA (Fig. 1.2).

Cteph Diagnosis And Image Analysis

Every patient assessed at our MDT meeting had been presumably diagnosed with CTEPH according to current CTEPH guidelines [3]. Nonetheless, differential diagnosis with alternative conditions was sometimes necessary for certain patients that presented with features mimicking CTEPH.

Our institution performed MCTA on a Philips Brilliance 64-slice computed tomographic (CT) scanner. Proximal disease was defined as lesions in the proximal main, lobar and proximal segmental arteries. Mid and distal segmental and subsegmental branches were considered peripheral disease.

An overall image quality assessment was performed for each study. The rating was determined by an optimal intravascular enhancement of vascular structures of more than 120 UH, a proper assessment of the whole pulmonary vasculature up to subsegmental branches with good signal-to-noise ratio, absence of motion artifacts and a slice thickness of 1 mm. Note that this study was conducted through a real-world practice setting with numerous externally referred CT exams. Therefore, optimal CT image quality could not be ensured for all of them.

As a national CTEPH referral center, at least 100 CTEPH cases have been evaluated annually over the last 4 years. All of the studies are analyzed by thoracic imaging unit radiologists, specialized in CTEPH assessment (minimum of 4 years' experience).

Intraoperative Cteph Classification And Hemodynamic Reassessment After Pea

Intraoperative classification of the thromboembolic disease using the one described by the UC San Diego group [12], was applied to every operated patient. Additionally, it served as an internal validation tool with our proposed noninvasive assessment of operability.

A systematic invasive hemodynamic evaluation was performed in all the patients one year after PEA.

Statistical analysis

The data are expressed as mean and standard deviation (normal distribution) and as median with a range (absence of normal distribution). Changes from baseline were evaluated with a paired t-test (continuous variables) and with χ^2 test (ordinal variables). Survival at 1 year after PEA and factors predicting outcome were analyzed using Cox proportional hazard regression. Significance was determined at $p < 0.01$.

Intra and interobserver variability were evaluated among a sample of 20% of optimal MCTA studies, regarding the level of agreement on the need to perform a complementary PA. For the intraobserver variability evaluation, 10 MCTA studies were selected and blindly reanalyzed with a 4–6 months lapse from prior analysis. For the interobserver variability evaluation, performed by 2 radiologists with the most (10 years) and the least (4 years) experience, 40 cases were individually and blindly evaluated.

Results

A total of 192 patients were prospectively evaluated from January 2016 to April 2018 at the MDT meeting: 89 patients in the first phase and 103 patients during the second phase.

Among the whole patient series, 16 patients were excluded from further analysis: 9 of them because of thromboembolic disease with no PH and the remaining 7 patients because of final diagnosis of PH secondary to alternative causes different from CTEPH, in which misdiagnosis of CTEPH had been drawn on V/Q lung perfusion defects. Final diagnosis among the latter was pulmonary veno-occlusive disease (PVOD) (4 patients), idiopathic PAH (1 patient), HIV-related PAH (1 patient) and lastly group 3 PH secondary to pneumoconiosis (1 patient).

Regarding patients with final diagnosis of PVOD, 1 of them presented disproportionately severe PH with an isolated subsegmental perfusion impairment alongside severely reduced diffusion lung capacity for carbon monoxide (DLCO). MCTA showed suggestive PVOD findings and PA helped to definitely rule out CTEPH. Genetic testing was positive for a biallelic mutation in EIF2 AK4 confirming PVOD. In the remaining 3 patients with a final diagnosis of PVOD, suspicion of CTEPH had been drawn on mismatched perfusion defects of V/Q scintigraphy with no CTEPH signs in advanced imaging. The patient with an HIV-related PAH form presented with an isolated segmental defect at pulmonary scintigraphy and in situ thrombosis and extensive calcification at various levels in the pulmonary vascular bed. The patient with a definitive diagnosis of idiopathic PAH had mismatched perfusion impairment on V/Q scintigraphy and no CTEPH signs in additional studies. Lastly, final diagnosis was group 3 PH secondary to pneumoconiosis in 1 patient, an occupational lung disease caused by the inhalation of dust in mines; which also presented with impaired perfusion at V/Q lung scan. PA was performed in all of these patients to adequately rule out CTEPH.

The average age of the cohort with a definitive diagnosis of CTEPH was 59, 1 (± 15 years old). 60% were women, with a mean mPAP of 47 mmHg (± 16 mmHg); 49% were in WHO functional class II and 48% in WHO functional class III.

Up to 89% of MCTA studies were considered optimal. The most frequent causes of suboptimal studies were: slice thickness greater than 3 mm (38%), poor opacification (25%), respiratory motion artifact (11%), obesity (9%) and improper breath-holding (9%) (Fig. 2).

For the need to perform a complementary PA based on MCTA findings, we found excellent intra and interobserver agreement, with square-weighted Kappa's of 0.8 a 0.85 respectively.

Decision Flowchart At Mdt Meeting

During the first phase, 50.6% of patients were initially deemed suitable for PEA based on MCTA imaging. Among them, the initial decision of operability was modified by PA only in one patient, where the absence of proximal disease at the PA compared to MCTA findings were attributed to a long-time lapse between

MCTA and PA performance. On the other hand, among patients judged inoperable based on MCTA imaging (28.2%), one patient was relocated as suitable for PEA after performing PA because of unobserved proximal disease at MCTA (Fig. 3.1).

Along the second phase, the operability decision was solely based on MCTA imaging in 49.4% of patients as they were overtly operable. In contrast, the remaining 50.6% of patients needed a PA to make the final operability decision in 26.4% of them, surgical assessment based on MCTA had not been possible (either because of suboptimal MCTA imaging or non-overt surgically amenable lesions at MCTA imaging) and 24.2% of them had been judged inoperable based on MCTA (Fig. 3.2).

Final Treatment, intraoperative classification and postoperative outcome.

Patients' disposition according to final treatment is summarized in Fig. 4. Amidst those patients who underwent PEA (n = 91), 18.7% had level I disease (Fig. 5.1), 45.1% level II disease, and 36.3% level III disease (Fig. 5.2). Table 1 summarizes the proportion of intervened patients in whose surgical decision was based either on MCTA vs those who needed a complementary PA, regarding intraoperative CTEPH classification. In up to 54% of intervened patients with level III disease, a decision on operability had been made exclusively on MCTA.

Table 1
Intraoperative CTEPH classification of intervened patients regarding initial operability assessment

Surgical classification	**Decision-based on MCTA n = 65**	**Complementary PA n = 26**
Level I disease (%)	94.1	5.9
Level II disease (n, %)	75.6	24.4
Level III disease (n, %)	54.5	45.5

Survival rates at 1-year after PEA in both initial and implementation phases of 93.7% and 95.4% respectively, were comparable in both phases of our study. Hemodynamic parameters at invasive reassessment at 1-year after surgery in both groups are shown in Table 2.

Efficiency Analysis And Safety Concerns

Shorter time periods to fulfill initial clinical assessment prior to the MDT meeting were achieved over the second implementation phase compared to those initially obtained (median waiting times of 110 days; IQR 32–172 vs 130 days; IQR 59–278; $p < 0.01$).

Among the 131 patients with CTEPH who underwent pulmonary angiography, minor complications occurred in three patients (2.3%): femoral hematoma that did not require transfusion (1 patient), allergic

reaction to iodine contrast with prompt response to medication (1 patient) and bleeding at the femoral access without transfusion requirements (1 patient). No deaths or major complications related to the technique occurred.

Discussion

To the best of our knowledge, this is the first study that addresses that a noninvasive assessment of operability is feasible in a substantial proportion of patients diagnosed with CTEPH.

The development of an optimized care process, was deemed essential for our institution, a national CTEPH referral center with up to 90% of external patients in order to make the surgical candidacy assessment for PEA more efficient in terms of shortened waiting periods, reduced costs and patients' displacements as well as increased patients' safety.

We obtained surgical rates of 65%, which were comparable to those previously reported in large series such as the large-scale, international registry of patients with CTEPH with surgical rates of 63% [13]. Additionally, our approach did not negatively impact surgical outcomes in terms of perioperative mortality and hemodynamic improvement at reassessment. Residual PH rates after PEA, which is widely established as a significant prognostic factor in terms of survival [14]; not only did not differ in both phases but tended to be lower in the implementation phase.

Our study aimed to deploy a novel surgical assessment for patients with CTEPH. With this scope, we observed that along the pilot phase, up to 50% of the patients deemed operable based on MCTA findings had been adequately classified as such, as PA did not modify the initial decision of operability in all but one of them (where the discrepancy between MCTA and PA findings were justified by a significant time lapse between both procedures). Additionally, comparable results were obtained along the second implementation phase in which surgical suitability was decided solely on MCTA in half of the patients. In the remaining patients, PA was still necessary to make a final operability decision ensuring that no operable patients were misclassified.

Our results indicate that PA was needed in up to 10.8% of the patients to adequately assess surgical candidacy because of suboptimal CT imaging. The proportion of optimal MCTA studies may be foreseeably improved by greater radiological expertise gained in external referral centers alongside with new-generation CT scanner equipment and improved examination protocols [15]. Moreover, CT will presumably gain popularity as a noninvasive hemodynamic monitoring tool in CTEPH as several CT scores have shown high correlation with hemodynamic parameters and surgical success rates [16].

It should be stressed that, CT imaging not only helps to evaluate vascular abnormalities that may suggest CTEPH but also alternative parenchymal or vascular disorders that may present with V/Q lung scanning defects. High incidence rates of positive V/Q studies (43,1%) have been reported in recent series among patients with no thromboembolic disease [17]. In our series, 4% of the patients referred as CTEPH

were based on impaired perfusion defects on V/Q scanning and displayed no thromboembolic disease in MCTA or in PA.

In order to perform an internal validation of the proposed operability assessment we sought to complete the performance analysis by determining the proportion of operated patients whose decision on surgical candidacy had been solely posed on MCTA. We observed that operability decision had been uniquely posed on MCTA not only in a high proportion of patients with levels I and II disease, but also in up to half of the patients with level III disease. These results, are consistent with previous studies, as the one conducted by Ley et al. in which, MCTA provided the highest image quality and level of sensitivities and specificities in segmental branches compared with the reference standard [15].

Furthermore, our approach attained significantly shorter time periods to fulfill a complete surgical assessment that consequently resulted in reduced time lapse periods to surgery.

Additionally, pulmonary angiography is an expensive procedure, with total costs that range from 4,084 to 6,738 Euros depending on the patients' severity profile [18]. Therefore, the constraint of this procedure to a restricted group of patients gains great relevance in national CTEPH referral centers as it leads to significant optimization in terms of costs as well as in cardiac catheterization laboratory availability.

Focusing on safety concerns, the avoidance of a PA in a considerable proportion of patients, enabled to avert an invasive exam not exempted from complications. Prior large series reported 1% rate of nonfatal major complications, 0.5% mortality rate and lastly, a 5% of minor complications rate [9, 10]. This significantly differed from complication rates obtained in our series, which might be explained by smaller sample size and additionally by growing expertise, more advanced catheters and less aggressive vascular approaches in recent years.

The limitation of this study follows from its single-center design so that multicenter studies are needed with larger cohorts in order to evaluate the reproducibility of our results. It must be noted that high CT imaging interpretative expertise is required in order to assure an adequate operability assessment and that our study did not aim to compare the validity of two radiological methods but to show real-world practice. Moreover, as the radiological assessment is focused on offering the most suitable treatment to every patient in order to avoid denying surgery to operable patients; this requirement at initial assessment probably introduces bias and reinforces the level of intra and interobserver agreement.

Conclusions

On the basis of our findings, we support the idea that a noninvasive surgical assessment in patients diagnosed with CTEPH is feasible not only in patients with levels I and II of the disease but also in a considerable proportion of patients with level III disease with no detrimental impact on postoperative outcomes. PA will still be necessary in approximately half of the patients with CTEPH in order to adequately determine surgical suitability as well as to guide and plan eventual balloon pulmonary angioplasty in non-operable patients.

This approach leads to an evolutionary enhancement of contemporary measures of performance such as quality of care, availability gain, efficiency and patient safety.

Abbreviations

CTEPH. - Chronic thromboembolic pulmonary hypertension.

PH.- Pulmonary hypertension

V/Q.- Ventilation-perfusion

MCTA. - Multidetector computed tomographic angiography

PA.- Pulmonary angiography

PEA. - Pulmonary endarterectomy

BPA. - Balloon pulmonary angioplasty

Declarations

Ethics approval and consent to participate

Institutional Review Board (Fundación Investigacion Doce de Octubre) approval was obtained. Written informed consent was obtained from all subjects (patients) in this study

Consent for publication

Consent to publish compute tomography (CT) studies and surgical specimens was obtained.

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Funding

The authors state that this work has not received any funding.

Competing interests

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article

Authors' contributions

ARC was in charge of the data analysis and major contributor in writing drafting of the manuscript. YRO analysed and interpreted compute tomography (CT) images and was in charge of manuscript supervision. MJLG performed both surgical specimen analysis and manuscript supervision. MTV analysed and interpreted pulmonary angiographies. IPDA conducted data collection and analysis. SAC was in charge of CT imaging analysis and interpretation. AAGT performed pulmonary angiography analysis. MPN analysed and interpreted CT Imaging. JLPV contributed to data collection and manuscript supervision. RMR conducted CT imaging analysis. JFDJ was in charge of manuscript supervision. FAY performed manuscript supervision. JMC was in charge of manuscript supervision. PES performed data interpretation manuscript supervision. All authors have read and approved the final manuscript

Acknowledgements

The authors acknowledge the whole cardiology, radiology, intensive care, cardiac surgery, pulmonology, physical therapy and nursing staff collaborating in the care of patients with CTEPH as well as the language editing of the paper performed by Talithia Richards.

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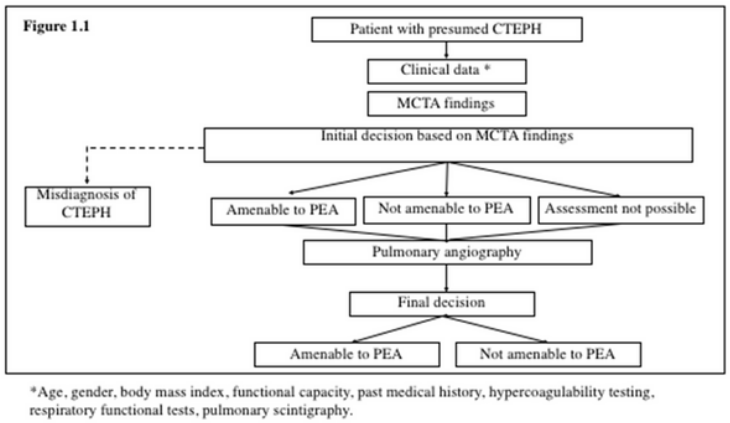
Figures



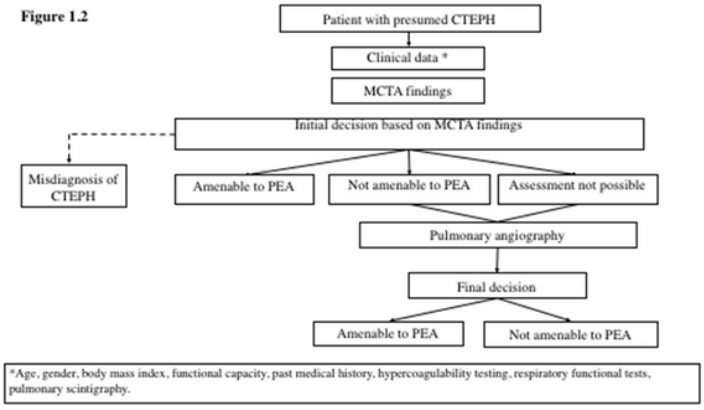


Figure 1

1.1.- Patient flow assessment performed along the first pilot phase. Every patient was assessed with both MCTA and PA at the MDT meeting. 1.2.- Patient flow assessment during the second “implementation” phase. PA was restricted to patients deemed inoperable based on CT or in patients in which assessment was not possible

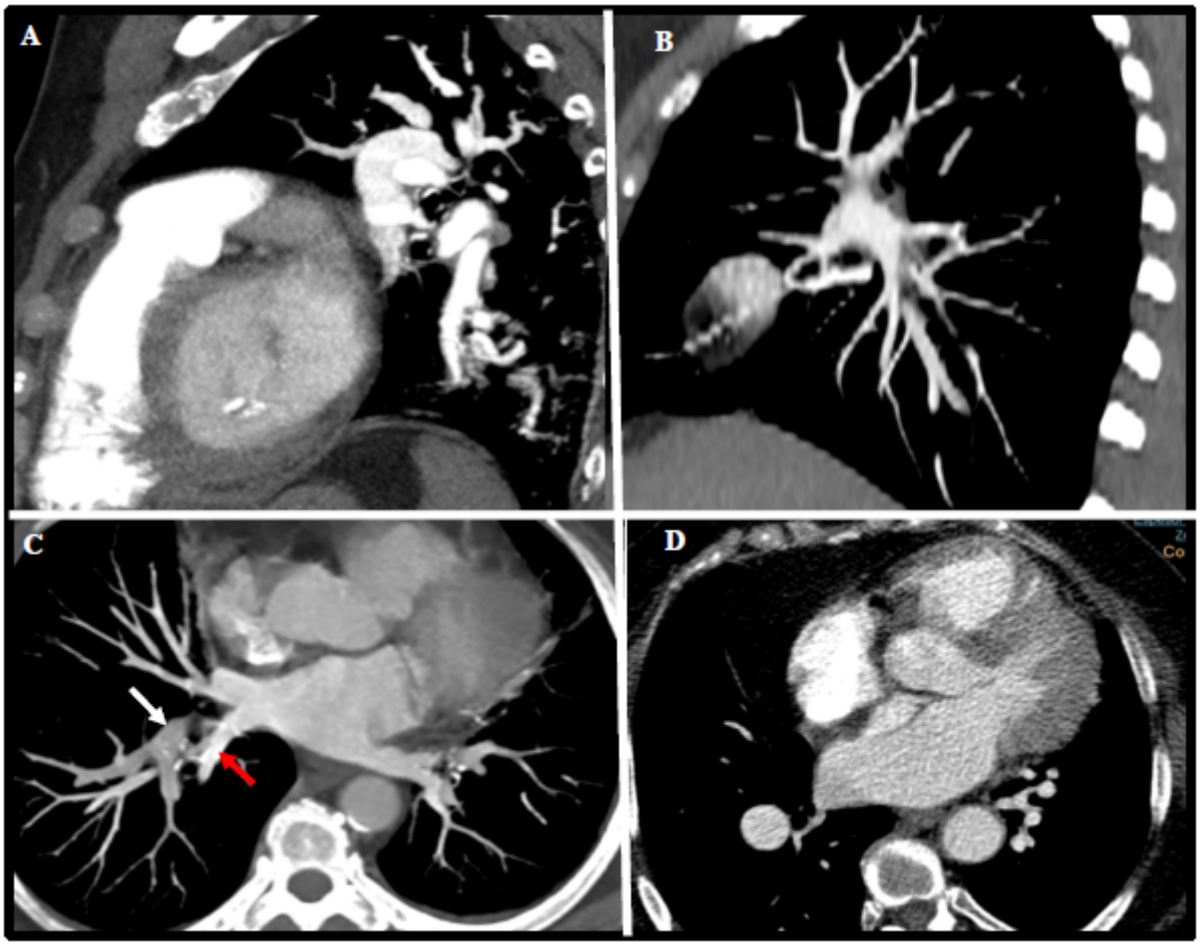
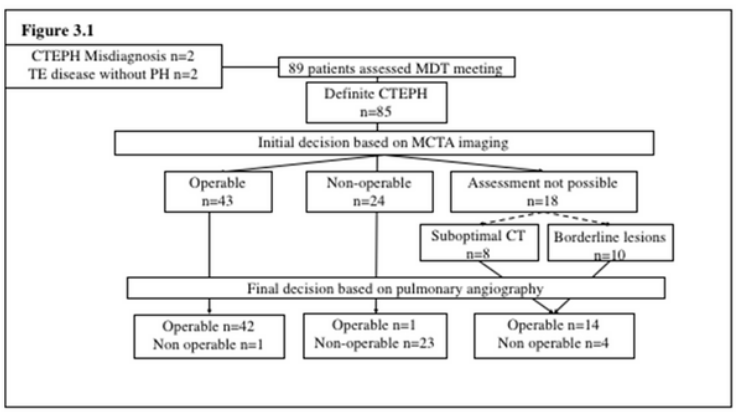


Figure 2

Common imagen artifacts found in MCTA. (A) Motion artifact at lower lobes. (B) CT stair artifact due to inadequate slice thickness. (C) Suboptimal contrast opacification of right upper lobe artery (white arrow) and inferior right vein (red arrow). (D) CT image noise in an obese patient.



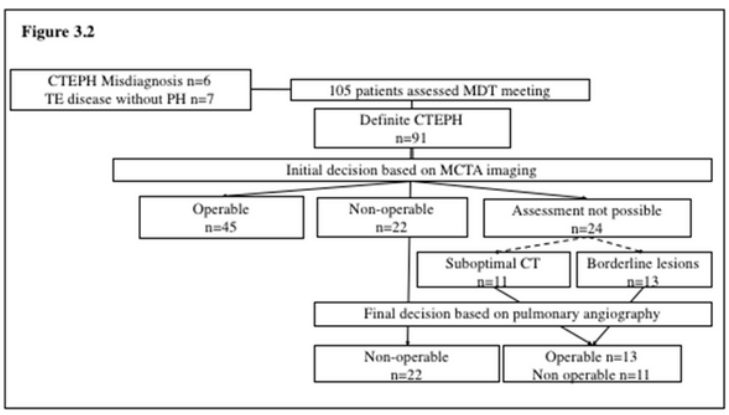


Figure 3

3.1.- Decision flowchart along the first phase. 3.2.- Decision flowchart along the implementation phase. CTEPH = Chronic thromboembolic pulmonary hypertension; TE= Thromboembolic; PH= Pulmonary hypertension; MDT=Multidisciplinary team; MCTA = Multidetector computed tomographic angiography; CT= computed tomography.

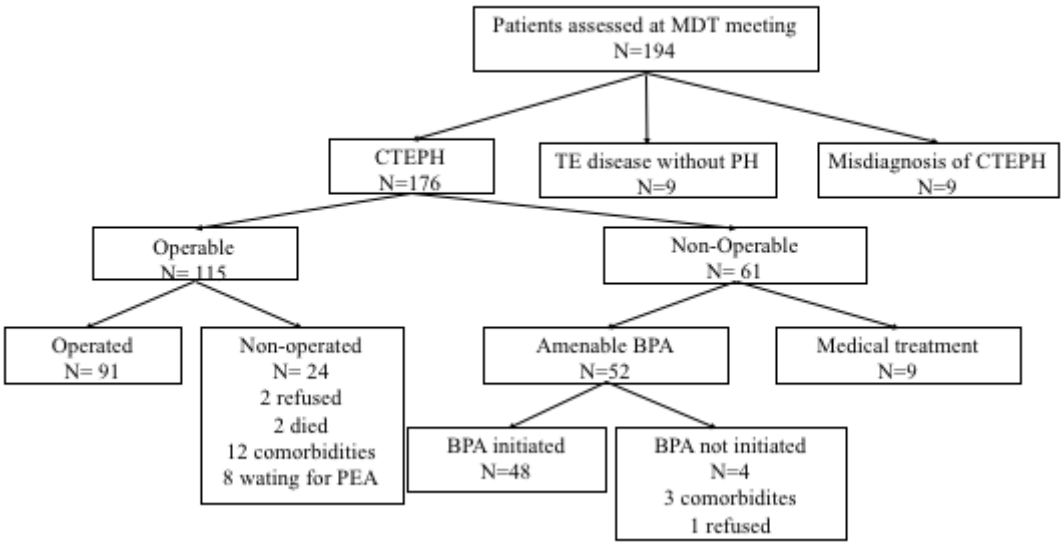


Figure 4

Patient's disposition according to final treatment.

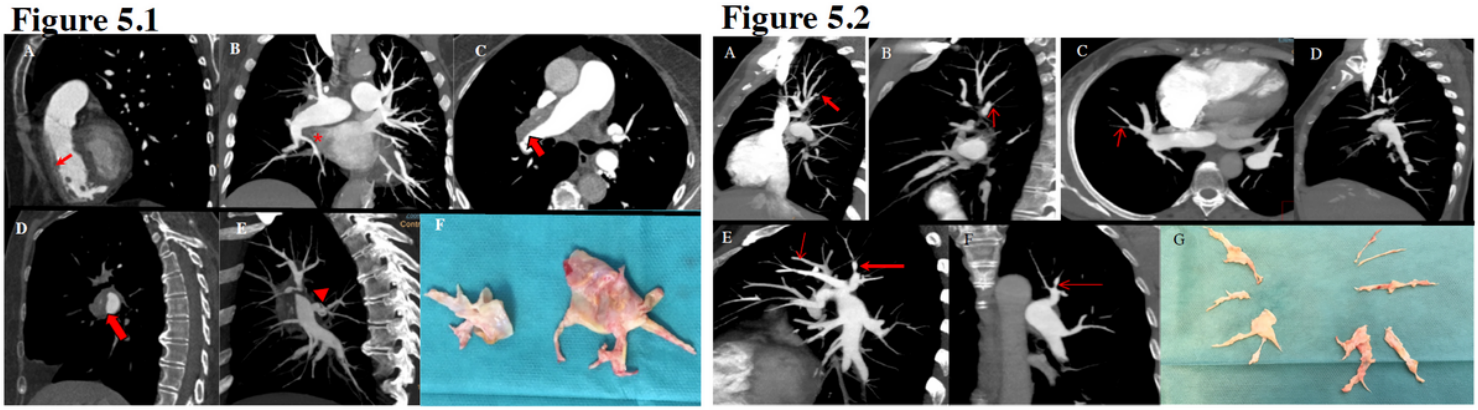


Figure 5

5.1.-Patient with proximal CTEPH. A, B Rectified interventricular septum (red thin arrow) and reduction of venous return (*).C, D, E Thromboembolic disease affecting the main pulmonary artery (red thick arrow) with extension to the right upper lobar artery (arrowhead). F Surgical specimen showing level I disease. 5.2.- Patient with distal CTEPH. G-L Organized intravascular material (thin red arrows) is identified at distal-segmental /subsegmental levels in all the pulmonary lobes. M Surgical specimen showing level III disease.

Table 2

Baseline and postoperative measures in operated patients

	Phase I (44)	Phase II (47)	p
Age (years)	56,74 ± 2,28	56,6 ± 1,76	ns
PAP mean prior PEA (mmHg)	46,87 ± 1,78	44,26 ± 2,01	ns
PVR prior PEA (UW)	7,55 ± 0,55	7,37 ± 0,64	ns
NT-proBNP (pg/ml)	1772 ± 428,34	1531,26 ± 291,97	ns
Pericardial effusion (n,%)	5 (11,36)	2 (4,2)	ns
6-MWD baseline (m)	508,81 ± 100,62	392,26 ± 20,93	ns
Surgical classification I (n,%) II (n,%) III (n,%)	9 (20,4) 20 (45,4) 15 (34,1)	9 (19,1) 23 (48,9) 15 (31,9)	ns
PAP m after PEA (mmHg)	32,17 ± 2,05	28,29 ± 2,52	ns
PVR after PEA (mmHg)	4,4 ± 0,54	3,78 ± 0,55	ns
Mean PAP m change (%)	-31,36	-36,08	ns
Mean PVR change (%)	-41,72	-48,71	ns
Residual PH after PEA n (%)	20 (46)	13 (27)	ns
Survival rate at 1 year after PEA	93,7%	95,4%	ns

PAP: Pulmonary artery pressure; PEA: Pulmonary endarterectomy; PVR: Pulmonary vascular resistance; 6-MWD: 6-minute walk distance; ns: non-significant ($p \geq 0,001$).