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Nicolas Piliero

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**L'ANGIOPLASTIE PULMONAIRE PERCUTANÉE POUR LE TRAITEMENT DE
L'HYPERTENSION PULMONAIRE THROMBOEMBOLIQUE CHRONIQUE :
RÉSULTATS DE L'EXPÉRIENCE INITIALE GRENOBLOISE**

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PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE

DIPLÔME D'ÉTAT

Nicolas PILIERO

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TABLE OF CONTENT

| | |
|--|----|
| <i>Abbreviations</i> | 13 |
| <i>Part I: Chronic Thromboembolic Pulmonary Hypertension: A Review</i> | 14 |
| Introduction | 15 |
| Epidemiologic data | 15 |
| Risk factors | 16 |
| Pathophysiology | 17 |
| Clinical presentation | 19 |
| Diagnosis | 19 |
| CTEPH screening imaging | 19 |
| CTEPH treatment assessment..... | 22 |
| Lesion type and classification | 22 |
| Health-related quality of life in CTEPH | 23 |
| Treatment | 25 |
| Treatment strategy | 25 |
| Medical treatment..... | 26 |
| Surgical Treatment..... | 28 |
| Interventional treatment..... | 30 |
| Prognosis | 32 |
| Gap of evidence | 32 |
| References | 33 |
| Supplementary files | 40 |
| <i>Part II: Balloon Pulmonary Angioplasty for the treatment of Chronic thromboembolic pulmonary hypertension: Results form the initial Grenoble Experience</i> | 42 |
| Introduction | 43 |

| | |
|--|------------------|
| Methods | 45 |
| Study design | 45 |
| Patients | 45 |
| Balloon pulmonary angioplasty | 46 |
| Measurements | 48 |
| BPA procedure-related complications | 49 |
| Radiation exposure | 50 |
| Systematic review | 50 |
| Statistical analysis | 51 |
| Results..... | 53 |
| Baseline characteristic | 53 |
| BPA procedures..... | 53 |
| Outcomes of BPA..... | 53 |
| Complications of BPA..... | 58 |
| X-ray exposure | 59 |
| Systematic review with meta-analysis..... | 60 |
| Discussion | 66 |
| Benefits of BPA..... | 66 |
| Complications and safety of BPA..... | 67 |
| Limitations of the study | 69 |
| Conclusion | 72 |
| Reference | 72 |
| Take-home figure | 75 |
| Supplementary files..... | 76 |
| <i>Resumés en Anglais et en Français.....</i> | <i>84</i> |
| <i>Conclusion de la thèse.....</i> | <i>86</i> |
| <i>Serment d’Hippocrate.....</i> | <i>88</i> |

TABLE OF FIGURES AND TABLES

PART I: Chronic thromboembolic pulmonary hypertension. A review

| | |
|--|----|
| Figure 1: Pathophysiology of CTEPH..... | 18 |
| Table 1: Risk factors of CTEPH..... | 17 |
| Figure 2: Algorithm for the screening of CTEPH..... | 20 |
| Figure 3: Example of typical finding of CTEPH lesion detected by V/Q planar scintigraphy..... | 21 |
| Table 2: The UCSD classification for surgical assessment of CTEPH..... | 23 |
| Figure 4: Health-related quality of life in CTEPH patient evaluated by Short Form 36..... | 24 |
| Figure 5: Algorithm for the treatment assessment of CTEPH..... | 25 |
| Table 3: Overview of majors RCTs evaluating medical treatment in CTEPH..... | 27 |
| Table 4: Overview of major studies evaluating the effects on hemodynamic and survival of PEA for the treatment of CTEPH..... | 29 |
| Table 5: Overview of studies (including more than 50 patients) evaluating BPA..... | 31 |
| Figure 6: Example of the treatment of the right inferior lobe by BPA..... | 40 |
| Figure 7: Example of Reperfusion Pulmonary Edema following BPA..... | 40 |

PART II: Chronic thromboembolic pulmonary hypertension. A review

| | |
|--|----|
| Figure 1: Major steps of a BPA procedure..... | 47 |
| Table 1: baseline characteristics..... | 54 |
| Figure 2: Major outcomes of BPA..... | 55 |
| Figure 3: Health-Related Quality of life evaluated by SF36v2..... | 56 |
| Table 2: Paired comparisons of Health-related quality of life outcome..... | 57 |
| Table 3: Cumulative incidence of procedure-related complications..... | 58 |
| Table 4: X-ray exposure..... | 59 |
| Figure 4: Prisma-style flow chart of the meta-analysis..... | 61 |

| | |
|---|----|
| Figure 5: Random-effect summary estimate for difference in 6-MWD at baseline and follow-up..... | 62 |
| Figure 6: Random-effect summary estimate for difference in mPAP at baseline and follow-up..... | 63 |
| Figure 7: Random-effect summary estimate for difference in PVR at baseline and follow-up..... | 64 |
| Figure 8: Random-effect summary estimate for difference in CI at baseline and follow-up ... | 65 |
| Table 5: paired comparisons of medical therapy use at baseline and follow-up.. | 77 |
| Table 6: Overview of primary studies of BPA for CTEPH..... | 78 |
| Figure 9: Random-effect summary estimate of hemoptysis incidence. | 81 |
| Figure 10: Random-effect summary estimate of pulmonary edema incidence. | 82 |
| Table 7: Comparison of radiation dose indicators for different cardiac procedures..... | 83 |

ABBREVIATIONS

6MWD: 6-Minute Walk Distance

BPA: Balloon Pulmonary Angioplasty

CTEPH: Chronic Thromboembolic Pulmonary Hypertension

CTPA: Computed Tomography Pulmonary Angiography

DECT: Dual Energy Computed Tomography

DSA: Digital Subtraction Angiography

INR: International Normalized Ratio

HRQOL: Health Related Quality Of Life

MLHFQ: Minnesota Living with Heart Failure Questionnaire

mPAP: Mean Pulmonary Arterial Pressure

PAH: Pulmonary Arterial Hypertension

PCWP: Pulmonary Capillary Wedge Pressure

PH: Pulmonary Hypertension

PE: Pulmonary Embolism

PEA: Pulmonary Endarterectomy

RHC: Right Heart Catheterization

SaO₂: Oxygen Saturation

SF-36: Short Form 36

SPECT: Single Photon Emission Computed Tomography

VKA: Vitamin-K Antagonist

V/Q: Ventilation/perfusion

PART I:
CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION:
A REVIEW

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) belongs to group 4 of the last classification of pulmonary hypertension (PH) ⁽¹⁾. It is defined by a pre-capillary PH secondary to pulmonary vascular obstruction by non-resolved thrombi at least 3 months after introduction of anticoagulation treatment. It leads to an increase in pulmonary vascular resistance, followed by progressive right ventricular dysfunction, leading to death in the absence of treatment ⁽²⁾.

Epidemiologic data

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but underestimated condition. A national audit of pulmonary hypertension in the United Kingdom and a Spanish registry evaluated its prevalence at between 10.8 and 38.4 per million population per annum and 19.2 cases per million adult inhabitants respectively ^(3,4). The incidence of CTEPH has been poorly evaluated, differs between countries, and has been reviewed in a recent article of *Gall H et al.* ⁽⁵⁾. If first reports of the incidence of CTEPH from Europeans registries were as low as 0.9 to 1.75 cases per year per million inhabitants ^(3,6,7), the real incidence of the disease is greater^(8,9) and the calculated incidence including diagnosed and undiagnosed disease ranges from 3 to 5 cases per year per 100000 inhabitants in the USA and Europe, and is around 2 cases per year per million inhabitants in Japan ⁽⁵⁾.

It has been well demonstrated that CTEPH follows a history of pulmonary embolism (PE) in 74.8 to 80.2% of cases ^(10,11). Several studies have focused on the incidence of CTEPH after an episode of PE. Results vary with between 0.3% to 8.8% of CTEPH diagnosis after a first episode of PE ⁽¹²⁻¹⁷⁾. In a recent review, *Ende-Verhaar YM et al.* showed that this difference might be the consequence of the difference in methods, duration of follow-up, criteria used for the diagnosis of CTEPH, and by the presence of biases ⁽¹⁸⁾. In this same study, the authors determined that the incidence of CTEPH was 3.21% of all survivors of PE. In a study

systematically screening CTEPH after a first episode of PE, 50% of patients with CTEPH were asymptomatic ⁽¹³⁾. Nevertheless, the interest of systematic screening for CTEPH after an episode of PE still need to be proved ^(15,19).

CTEPH is underdiagnosed for multiple reasons, including the relatively unspecific symptoms of the disease, nonuniformity of the diagnosis and physicians who are ill-informed about the disease ⁽¹⁹⁾. It has also been shown that a part of the patients diagnosed as having CTEPH have systolic pulmonary arterial pressure higher than 60mmHg at the diagnosis of PE, suggesting an existing CTEPH condition ^(17,20). Moreover, in the different registries, the time between PE and diagnosis of CTEPH is relatively short, which is in disagreement with the classic “honey moon” of the disease.

In the various registries, CTEPH is mostly diagnosed between 50 and 70 years of age with males and females both being equally affected ^(3,4,6,7,10,21,22).

Risk factors

Several thrombotic and non-thrombotic risk factors have been detected and are summarized in *table 1*. It has been shown that plasma factor VIII was elevated in CTEPH patients compared to both controls and pulmonary arterial hypertension (PAH) and was not modified by pulmonary endarterectomy (PEA) ⁽²³⁾. One study revealed a higher frequency and a higher titre of phospholipid-dependent antibodies in the CTEPH group than in the PAH group ⁽²⁴⁾. *Wong CL* et al. found similar results concerning plasma factor VIII but didn't find a significant difference in phospholipid-dependent antibodies between CTEPH and non-CTEPH patients. In the same study, more patients in the CTEPH group had elevated Von Willebrand factor, and more were heterozygous for Leiden factor V in the CTEPH group than in the non-CTEPH group, confirming that both hereditary and acquired thrombotic risk factors are implicated in CTEPH ⁽²⁵⁾.

Besides these thrombotic risk factors, several medical conditions including splenectomy, a ventriculo-atrial shunt, hydrocephalus, chronic inflammatory disorders, non-O blood group, infected pacemaker, thyroid replacement therapy, a history of malignancy and previous venous thromboembolism or recurrent VTE have been associated with an increased risk of CTEPH (26,27).

It has also been shown that in patients with acute PE, a high perfusion defect, an absence of aetiology (idiopathic PE), and a previous PE are risk factors for CTEPH (12).

Table 1: Risk factors of chronic thromboembolic pulmonary hypertension

| Thrombotic risk factors | Non-thrombotic risk factors | Previous PE risk factors |
|-----------------------------------|------------------------------------|---------------------------------|
| <i>Hereditary</i> | Splenectomy | High perfusion defect |
| Elevation of factor VIII | Ventriculo-atrial shunt | Idiopathic PE |
| Elevation of vWF | Hydrocephaly | |
| Heterozygous factor V Leiden | Chronic inflammatory disease | |
| phospholipid-dependant antibodies | Non-O blood groups | |
| <i>Acquired</i> | Infected pacemaker | |
| Recurrent VTE | Thyroid replacement therapy | |
| Previous venous thromboembolism | History of malignancy | |
| | Central venous catheter | |

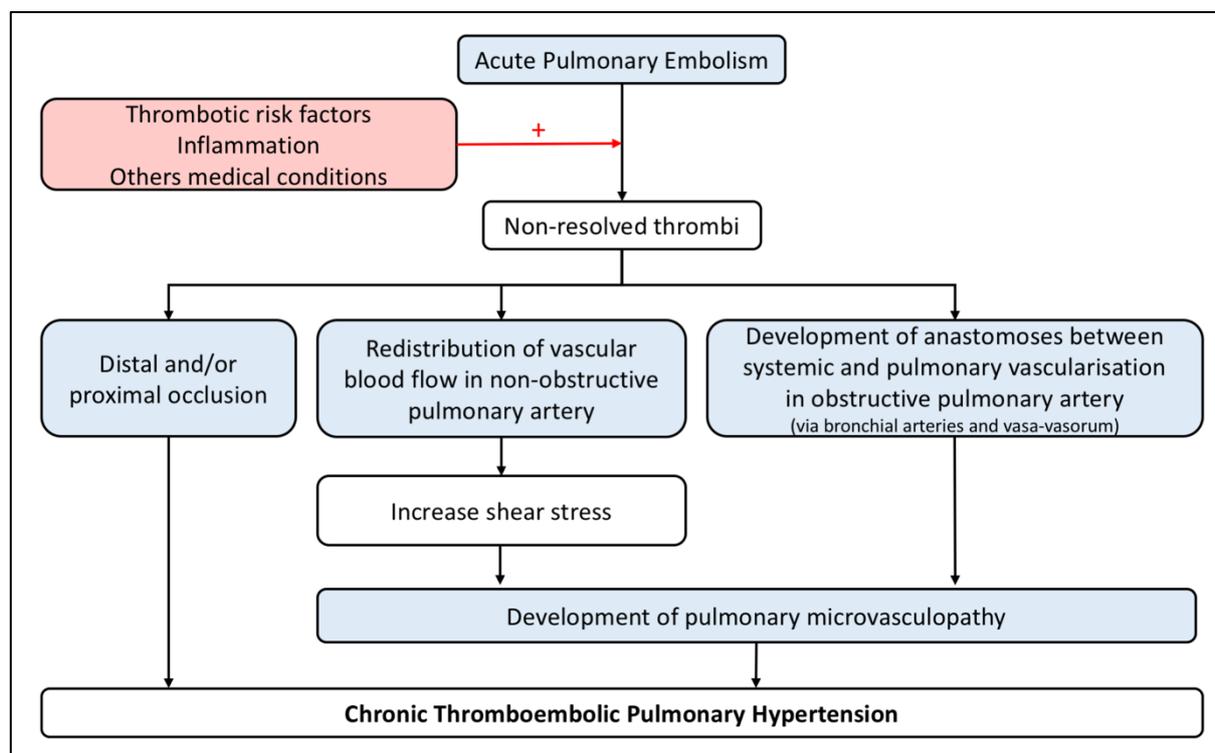
Pathophysiology

The pathophysiology of CTEPH is still not completely understood; it is complex and multifactorial including pulmonary artery obstruction by non-resolved thrombi, and pulmonary microvasculopathy (*figure 1*).

Indeed, the first stage of the disease is the non-resolution of thrombi following PE leading to total vascular obstruction and/or pulmonary artery stenosis. This non-resolution of

thrombi might be aggravated by the above mentioned thrombotic risk factors, in particular the factor VIII / Von Willebrand factor complex, but also by chronic inflammation, fibrinogen and fibrinolytic abnormalities and alteration in angiogenesis ^(20,28,29). *Quarck R*, demonstrated in two different studies that not only C-reactive protein but also other inflammatory mediators such as interleukin-10, monocyte chemotactic protein-1, macrophage inflammatory protein-1 α and matrix metalloproteinase-9 were elevated in CTEPH patients, which suggests a significant implication of inflammation in the genesis of CTEPH ^(30,31). Furthermore, resistance of fibrin to plasmin-mediated lysis has been highlighted in CTEPH patients ⁽³²⁾. Moreover, *Yaoita N* et al. found an elevated level of thrombin-activated fibrinolysis inhibitor in CTEPH patients, a factor implicated in the inhibition of fibrinolysis, and this level was unchanged by pulmonary balloon angioplasty ⁽³³⁾.

Figure 1: Pathophysiology of Chronic Thromboembolic Pulmonary Hypertension



Secondary to pulmonary obstruction, small pulmonary vessel disease has been detected in CTEPH. This was first described in 1993 by *Moser and Bloor* who found on histopathologic

examination of lung tissue from a CTEPH patient similar abnormalities as in PAH, like media hypertrophy, eccentric intimal fibrosis, concentric laminar intimal fibroelastosis, and internal fibromuscular proliferation ⁽³⁴⁾. These abnormalities are visible both in muscular pulmonary arteries but also in arterioles and venules, and can be explained by an elevation of the shear stress in non-occluded pulmonary arteries, secondary to hypertension and the redistribution of blood flow ^(20,35). Moreover, small pulmonary vessel disease has also been detected distal to an occluded pulmonary artery and could be due to bronchial to pulmonary shunting. Indeed, it has been clearly demonstrated that bronchial arteries are dilated in CTEPH ⁽³⁶⁾, and this might be explained by re-opening of anastomoses between the systemic and pulmonary artery circulation via hypertrophic bronchial arteries and vasa-vasorum ^(35,37,38). This shunting could exist both at the capillary and post-capillary level, leading to lesions similar to hemangiomatosis and pulmonary veno-occlusive disease respectively ⁽²⁰⁾.

Clinical presentation

Patients with CTEPH have unspecific symptoms that are common to all pulmonary hypertension disorders. In an international registry of CTEPH patients from Europe and Canada the most frequent symptoms were dyspnoea in 99.1%, oedema in 40.5%, fatigue in 31.5%, chest pain in 15.3% and syncope in 13.7% ⁽¹⁰⁾.

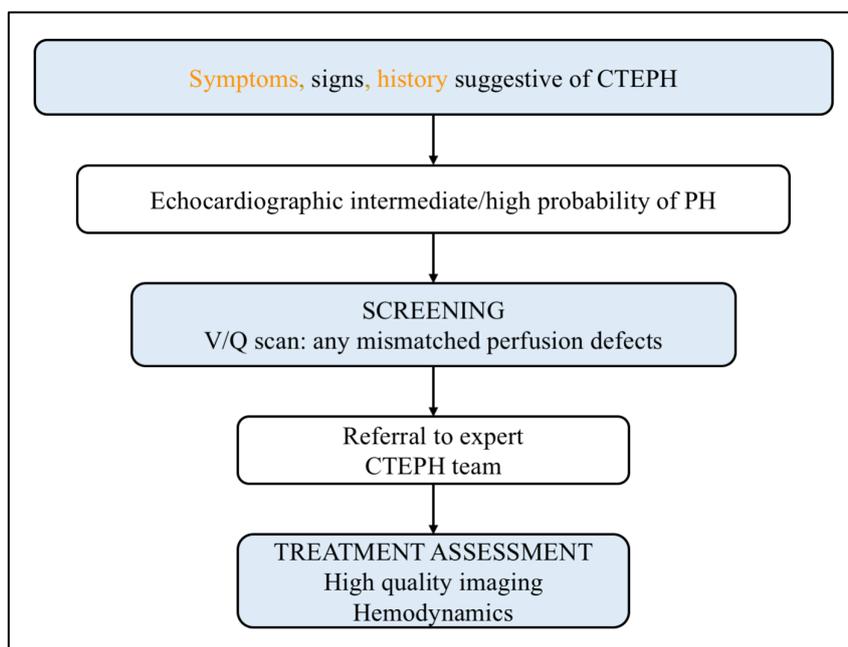
Diagnosis

CTEPH screening imaging

In the above-mentioned guidelines and in the algorithm presented during the 6th (most recent) symposium on Pulmonary hypertension (*figure 2, unpublished data*), the first step for the screening of CTEPH in patients with symptoms or a history suggestive of CTEPH is to perform echocardiography. Findings in favour of CTEPH are common with all types of pulmonary hypertension. They associate elevation of peak tricuspid regurgitation velocity over

3.4m/s or over 2.8m/s associated with other signs of PH such as dilatations of the right heart cavities and/or pulmonary arteries.

Figure 2: Algorithm for the screening of chronic thromboembolic pulmonary hypertension

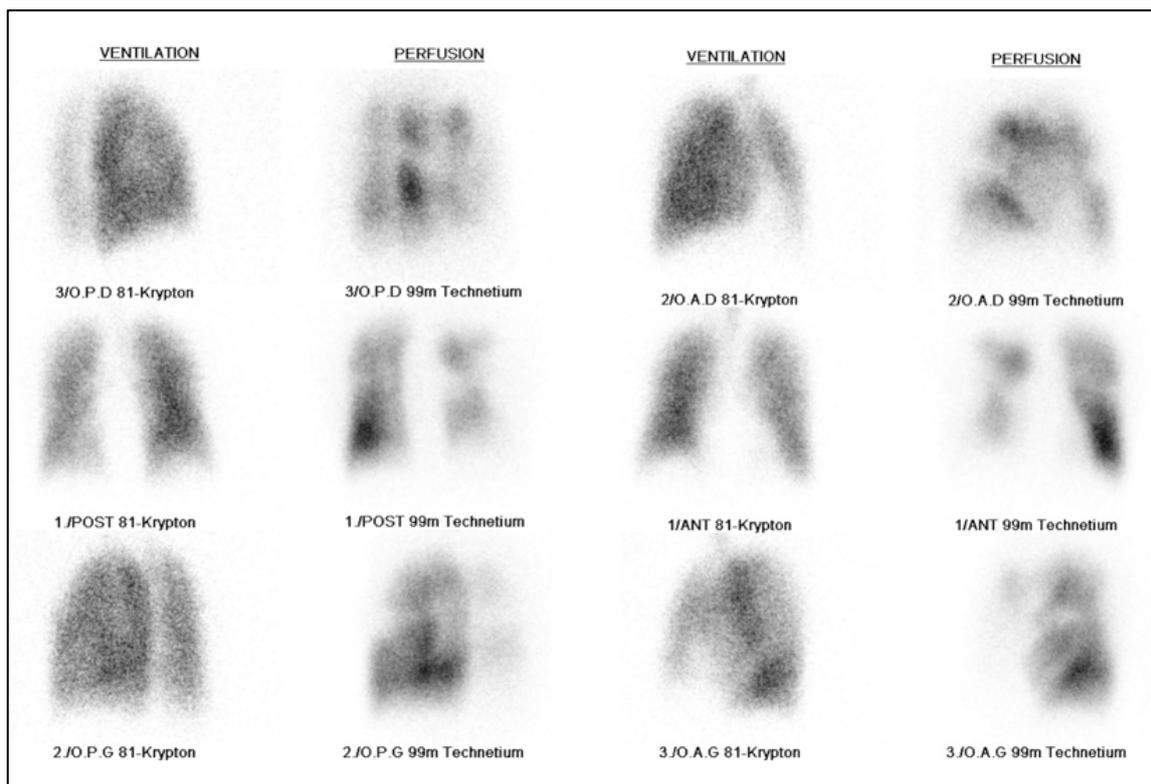


Abbreviations: CTEPH=Chronic thromboembolic Pulmonary Hypertension, PH=Pulmonary Hypertension, V/Q scan=Ventilation/perfusion scintigraphy

When echocardiography suggests an intermediate or high risk of CTEPH, the next step is the realisation of ventilation/perfusion (V/Q) scintigraphy, the method of choice for the detection of CTEPH. V/Q scintigraphy allows one to detect perfusion defects without ventilation abnormalities (also called V/Q mismatch) secondary to the vascular obstruction caused by CTEPH (figure 3). Conventional planar V/Q scintigraphy is progressively being replaced by single photon emission computed tomography (SPECT) V/Q which probably increases the sensitivity and specificity of the diagnosis, even if it has been better validated in PE than in CTEPH (19).

When a V/Q mismatch is present, the patient should then be referred in a CTEPH expert centre to confirm the diagnosis of CTEPH and to perform further examinations to assess the treatment.

Figure 3: Example of typical finding of CTEPH lesion detected by V/Q planar scintigraphy



Typical V/Q planar scintigraphy finding in CTEPH: Ventilation is normal in both lung, but perfusion is altered with multiple perfusion defect, bilateral but predominant in the right lung, typical of CTEPH lesions. Abbreviations: OPD=Right Posterior Oblique view; POST=Posterior view; OPG=Left Posterior Oblique view; OAD=Right Anterior Oblique view; ANT=Anterior view; OAG=Left Anterior Oblique view.

Other modalities have been evaluated for the screening of CTEPH but are not recommended at present. Cardiopulmonary exercise testing has been evaluated in one study, and might be of interest for screening CTEPH in patients with normal echocardiography (39). Several studies have evaluated computed tomography pulmonary angiography (CTPA) for the screening of CTEPH, with contradictory results. *He J et al.* found similar performance between V/Q scintigraphy and CTPA with a sensitivity and specificity of 92.2 and 95.2% respectively for CTPA (40). In contrast, *Tunariu N et al.* reported weaker sensitivity of CTPA compared to V/Q scintigraphy with a sensitivity of 51% and specificity of 99% for CTPA and a sensitivity of 96% and specificity of 90% for V/Q scintigraphy (41). Dual energy computed tomography (DECT) has recently been evaluated for the detection of CTEPH. DECT seems to be a valuable

technique for the detection of CTEPH with a sensitivity between 96 and 100% and a specificity between 92 and 96% (42,43). Nevertheless, this technique is still under evaluation and should be performed in an expert centre only, especially because of iodine-defects (44).

CTEPH treatment assessment

Right heart Catheterization (RHC) is still mandatory for the diagnosis of CTEPH, and to confirm the existence of precapillary pulmonary hypertension, with a mPAP \geq 25mmHg and a pulmonary capillary wedge pressure (PCWP) $<$ 15mmHg (45). The measurement of PCWP can sometimes be made difficult by vascular obstruction. In this case, measurement of left ventricle end-diastolic pressure by left heart catheterization might be an alternative (19).

RHC is most of the time associated with the realisation of a selective digital subtraction angiography (DSA). Selected DSA has a key role in the management of CTEPH, as it permits to assess the localization and type of lesions which are two major criteria for the decision to operate (19,46,47). More recently, several studies have evaluated the benefits of cone-beam computed tomography for the detection and classification of CTEPH lesions before the treatment decision. Results were encouraging with a good detection and classification of distal lesions which is particularly interesting when a percutaneous treatment is decided (48,49).

Lesion type and classification

Selective DSA at segmental and sub-segmental levels during interventional procedures, as well as new imaging techniques like cone-beam computed tomography have given us a better comprehension of the lesions present in CTEPH at the intra-vascular compartment. This has also been illustrated by intra-vascular optical coherence tomography imaging, which detected different types of CTEPH lesions (50–52). *Kawakami T et al.* suggested a novel classification of vascular lesions in CTEPH based on selective angiogram divided into five categories: type A,

ring-like stenosis lesion; type B, web-like lesion; type C, subtotal lesion; type D, total occlusive lesion and type E, tortuous lesion ⁽⁵³⁾. Type A to type D lesions are proximal to the sub-segmental artery, whereas type E lesions are distal to the sub-segmental artery.

Another classification, based on the location of the thromboembolic disease rather than on the type of lesion has also been proposed by the University of California, San Diego (UCSD Classification) and is particularly relevant for surgical assessment ⁽⁵⁴⁾. It classifies the thromboembolic disease in five levels where 0 corresponds to no lesions and IV corresponds to thromboembolic lesions starting at the sub-segmental branches only (*table 2*).

Table 2: The UCSD classification for surgical assessment of CTEPH

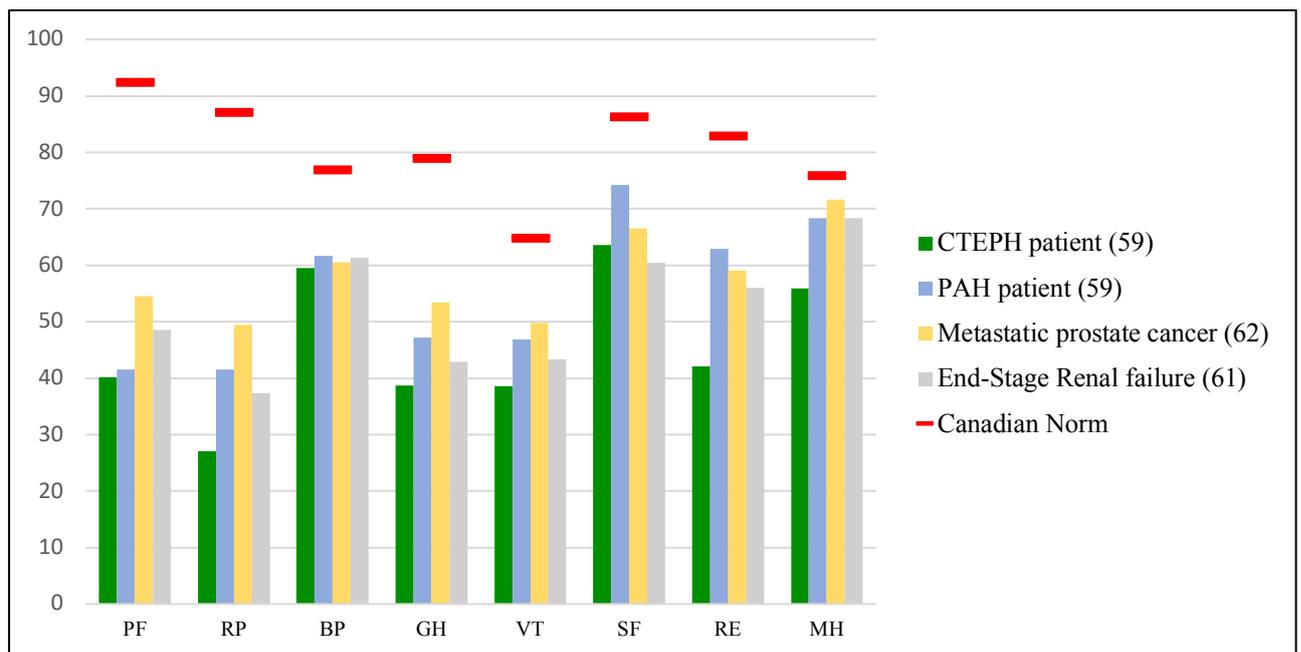
| Surgical level | Location of thromboembolic disease |
|-----------------------|--|
| 0 | No evidence of thromboembolic disease |
| I | Starts in the main pulmonary arteries patients with complete occlusion of one lung are classified as level IC |
| II | Starts at the level of the lobar or intermediate pulmonary arteries |
| III | Starts at the level of segmental arteries only |
| IV | Starts at the subsegmental branches only |

Health-related quality of life in CTEPH

Few data are available concerning health related quality of life (HRQOL) in the CTEPH population and most are derived from data including both CTEPH and PAH or pulmonary artery disease patients ⁽⁵⁵⁾. General evaluation of HRQOL by a generic scale such as the short-form 36 (SF36) showed that HRQOL is markedly altered in both CTEPH and PH populations^(56–59) and more severely altered than in other chronic conditions such as chronic broncho-obstructive pulmonary disease ⁽⁶⁰⁾, end stage renal failure ⁽⁶¹⁾, or metastatic prostate cancer ⁽⁶²⁾, as previously demonstrated for PAH ^(63,64) and illustrated in *figure 4*. The only two studies which compared HRQOL in CTEPH patients with PAH s found similar or worse results for CTEPH patient but this result should be taken with precaution because of the low sample

size of the population (56,59). Interestingly, *Taichman et al.* noted that in PAH patients, the physical component summary was better in patients without oxygen and diuretics, and that both emotional and physical summaries of SF36 were correlated with the 6MWD but not with hemodynamics (63). Three studies evaluated HRQOL in CTEPH patients before and after PEA (59–61) and one before and after BPA (65), and found similar results at baseline with good improvement after the procedures. These results were confirmed with other non-PAH-specific tools like the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (66,67) and with PAH-specific instruments such as the CAMPHOR questionnaire (68). This severe alteration in HRQOL is often associated with anxiety and depression disorders, revealed with a specific questionnaire, and is all the more severe as depression and/or anxiety symptoms become worse(57,59,67).

Figure 4: Health-related quality of life in CTEPH patient evaluated by Short Form 36



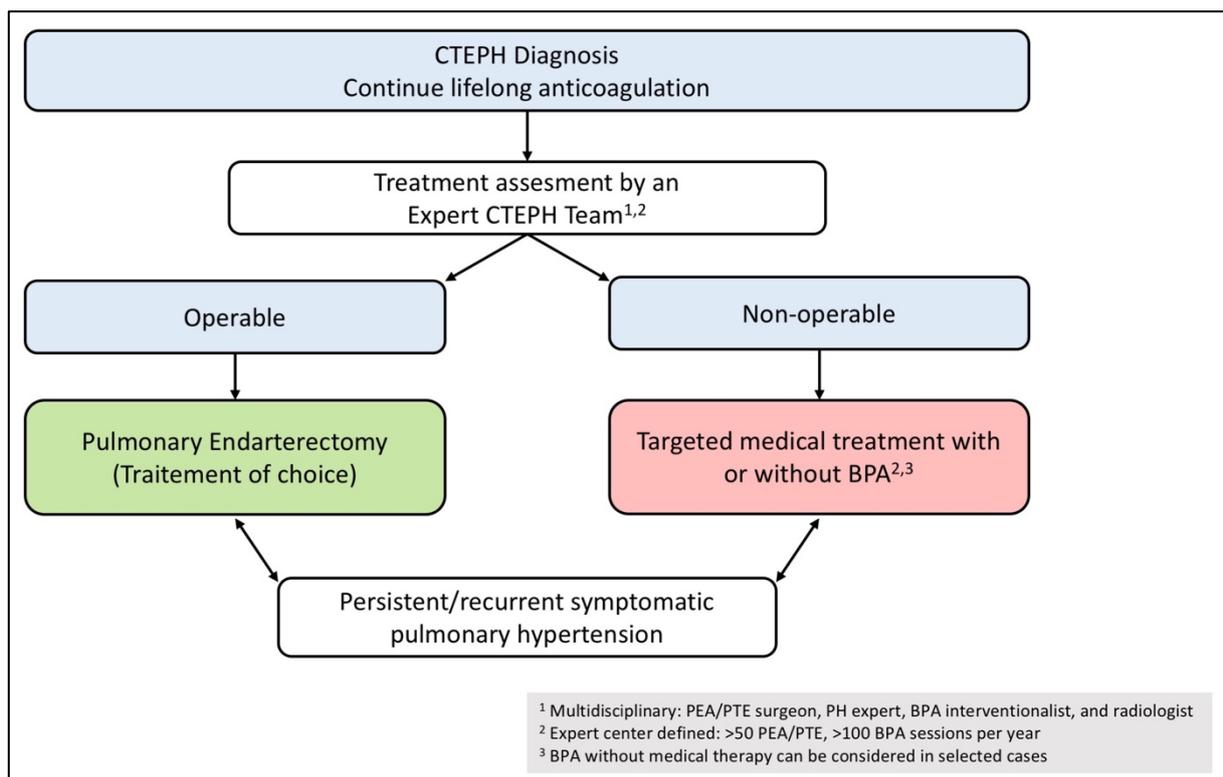
Abbreviations: PAH=Pulmonary Arterial Hypertension; PF=Physical Functioning; RP=Role-Physical; BP=Bodily Pain; GH=General Health; VT=Vitality; SF=Social Functioning; RE=Role-Emotional; MH=Mental Health. Higher scores indicate better perceived health status.

Treatment

Treatment strategy

The treatment of CTEPH depends on the accessibility of the obstruction, comorbidities of the patient, age, and previous treatment. Currently, the treatment of choice is still pulmonary endarterectomy (PEA), which should be performed whenever possible. Alternatives are medical treatment and/or pulmonary balloon angioplasty (BPA). All patients' treatment must be discussed by an expert multidisciplinary CTEPH team including a PH expert, a surgeon who perform PEA, a radiologist, and an interventional cardiologist who performs BPA. The algorithm proposed by the 6th World Symposium on Pulmonary Hypertension is shown in [figure 5 \(unpublished data\)](#).

Figure 5: Algorithm for the treatment assessment of CTEPH



Abbreviations: BPA=Balloon Pulmonary Angioplasty; CTEPH=Chronic Thromboembolic Pulmonary Hypertension; PEA=Pulmonary endarterectomy; PTE=Pulmonary Thromboendarterectomy

Medical treatment

Randomized controlled trials (RCT) evaluating medical therapy for CTEPH are summarized in [table 3](#). Currently, Riociguat is the only treatment licensed for CTEPH in Europe. It has been validated by the CHEST-1 study which demonstrated an improvement in 6MWD of 39m (primary outcome) and a reduction in PVR of 28% versus placebo at week 16 ⁽⁶⁹⁾. Long-term outcomes of this treatment have been evaluated in the CHEST-2 study which confirm the long-term benefits and safety of this treatment ⁽⁷⁰⁾. Others RCT have evaluated PAH medication for CTEPH. Sildenafil has been tested versus placebo in a small population of CTEPH, but the results were not positive for the primary outcome ⁽⁷¹⁾. Bosentan has been evaluated in the BENEFit study and showed an improvement of one of the two primary outcomes (Change in PVR and/or in 6MWD from baseline to week 16) with a reduction in PVR of 24%, but with a non-significant change in 6MWD ⁽⁷²⁾. Finally, more recently Macitentan has been evaluated versus placebo in the MERIT-1 study. The study was positive with a reduction of PVR of 27% at week 16 (primary outcome) and also showed a benefits on 6MWD (+35m), NYHA functional class and NTpro-BNP ⁽⁷³⁾. Off-label drugs are used in routine practice in similitude to PAH even if they have not been clearly evaluated ⁽⁷⁴⁾. Use of medical treatment as bridging therapy for PEA or BPA is also frequently used in practice but has not been evaluated yet.

Table 3: Overview of majors randomized controlled trials evaluating medical treatment in CTEPH

| Author, y | Suntharalingam J, 2008 | Jais X, 2008 | Ghofrani HA, 2013 | Simonneau G, 2014 | Ghofrani HA, 2017 |
|-----------------------------------|---|---|---|---|--|
| | | BENEFiT | CHEST-1 | CHEST-2 | MERIT-1 |
| Country | United Kingdom | International | International | International | International |
| No Study sites | 1 | Muticentric | 89 | 89 | 48 |
| Treatment | sildenafil vs placebo | bosentan vs placebo | riociguat vs placebo | riociguat | macitentan vs placebo |
| Enrolment Period | 2004-2007 | | 2009-2012 | | 2014-2016 |
| n | 19 | 157 | 261 | 237 | 80 |
| Primary outcome | Change in 6MWD from baseline to week 12 | Change in PVR and/or in 6MWD from baseline to week 16 | Change in 6MWD from baseline to week 16 | long-term safety and tolerability at 1 year | Change in PVR from baseline to week 16 |
| Positivity of the primary outcome | No | Yes | Yes | - | Yes |
| Reduction of PVR, % | -22 | -24,1 | -28,6 | - | -27 |
| Change in 6MWD, m | 18 | 2,9 | 39 | 51 | 35 |
| Improvement in NYHA, % | 29,4 | 14,5 | 15 | 50 | 15 |
| Change in NT-proBNP, pg/mL | -355 | -622 (treatment effect) | -291 | -416 | -651 |

Abbreviations: 6MW=6-minute Walk Distance; BNP=Brain Natriuretic Peptide; NYHA=New York Heart Association Functional Class; PVR=Pulmonary Vascular Resistance.

Surgical Treatment

PEA is the recommended treatment for CTEPH according to the recent guidelines endorsed by the European Society of cardiology and European respiratory society ⁽⁴⁵⁾. PEA surgery is a difficult and complex surgery which requires sternotomy, cardio-pulmonary bypass and deep hypothermic cardiac arrest. It consists of a complete dissection in the plane of the media of the 2 pulmonary arteries extending to the distal vessels, allowing a complete endarterectomy ⁽⁷⁵⁾. Results from major recent studies evaluating PEA are summarized in [table 4](#). This surgery must be performed by a highly trained surgeon working in a specific CTEPH-team and each case must be discussed by a multidisciplinary team to obtain the best results ⁽⁵⁴⁾. Indeed, PEA surgery has several limitations. First of all, in an international registry, only 60% of CTEPH patients were eligible for PEA ⁽¹⁰⁾ and this data has been confirmed by several monocentric observational studies ^(6,76). Nevertheless, it has been shown that operability for PEA depends largely on the PEA-team ⁽⁷⁷⁾, and it is recommended to refer non-eligible patients to a second PEA-team to confirm the decision ⁽⁷⁸⁾. Moreover, two recent studies have shown the feasibility of PEA in the elderly, with a slightly higher rate of in-hospital death ^(79,80). One study also demonstrated the feasibility of PEA in patients with a distal form ⁽⁸¹⁾. The second limitation of PEA is the relatively high risk of the surgery. Indeed, first reports of PEA revealed an in-hospital mortality of between 11.5 and 17.5% and a 3-year survival between 76 and 81% ^(6,82-85). Cannon *JE et al.*, reported long-term survival of 72% ten years after PEA ⁽⁸⁶⁾. However, a learning curve effect has been well demonstrated in several studies ^(87,88), and actual in-hospital mortality is evaluated at 5.4% in the international registry ⁽⁷⁴⁾, and as low as 2.2 to 2.5% in the most recent single-centre observational studies ^(76,89). Finally, the last limitation of PEA is residual PH in some patients after the procedure, leading to a worst outcome. No recommendations exist for the management of this particular population, although repeat surgery should not be performed excepted in exceptional cases. Two small sample studies reported the possibility of repeat surgery but it was associated with higher risk of post-procedural death^(90,91).

Table 4: Overview of major studies evaluating the effects on hemodynamic and survival of pulmonary endarterectomy for the treatment of CTEPH

| Author, y | Corsico AG, 2008 | Condliffe R, 2008 | Korsholm K, 2017 | Delcroix M, 2016 | Berman M, 2012 | Lankeit M, 2017 |
|--------------------------|----------------------------------|---------------------------------|---------------------------------|------------------|---|-----------------------------------|
| Country | Italy | United Kingdom | Denmark | International | United Kingdom | Germany |
| No Study sites | 1 | 5 | 1 | 27 | 1 | 1 |
| Enrolment Period | 1994-2006 | 2001-2006 | 1994-2016 | 2007-2009 | 2006-2011 | 2014-2015 |
| n | 157 | 236 | 239 | 404 | 411 | 237 |
| Age, y | 55 ± 16 | 57,6 ± 15,6 | 60 ± 12,8 | 55,5 ± 11,6 † | 56,9 ± 15,5 | 62 ± 14,9* |
| % female | 45,9 | 47 | 45 | 45 | 45,7 | 46 |
| Operability, % | - | 52 | - | 60 | - | 65,3 |
| Evolution mPAP, mmHg | 47,6 ± 12,9 to 23,9 ± 10,9 | 48,2 ± 10,1 to 26,8 ± 9,8 | 48,4 ± 10,7 to 33,4 ± 8,9 | - | 49,2 ± 13,5 to 27 ± 9,6 for patients <70ans 43,6 ± 10,5 to 29,1 ± 10,1 for patients >70ans | 42,3 ± 11,9* to 29,3 ± 5,2* |
| Evolution PVR, WU | 14,3 ± 6,5 to 4,1 ± 3,0 | 12,9 ± 5,3 to 5,8 ± 2,7 | 10,7 ± 5,0 to 4,4 ± 2,9 | - | 8,7 ± 4,7 to 3,8 ± 3,2 for patients <70ans 7,9 ± 4,1 to 4,9 ± 3,6 for patients >70ans | 7,5 ± 4,0* to 4,9 ± 2,2* |
| In-hospital mortality, % | 11,5 | 16 | 8,4 | 4,7 | 4,6 for patients <70ans 7,8 for patients >70ans | 2,5 |
| 1-year survival, % | 96 | 88 | - | 93 | 91,4 for patients <70ans 85,9 for patients >70ans | - |
| 3-year survival, % | - | 76 | 77 | 89 | 87,5 for patients <70ans 84,1 for patients >70ans | - |

Abbreviations: mPAP=mean Pulmonary Arterial Pressure; PVR=Pulmonary Vascular Resistance. Values are expressed in mean ± standard deviation.

*Mean and standard deviation values were computed according to Wan et al (BMC Med Res Methodol. 2014 Dec 19;14:135.) from median and interquartile range.

†Mean and standard deviation values were computed according to Wan et al (BMC Med Res Methodol. 2014 Dec 19;14:135.) from median and minimum and maximum values.

Interventional treatment

Besides PEA and medical treatment, balloon pulmonary angioplasty (BPA) has emerged in the last 10 years as a novel therapy for the treatment of CTEPH.

Briefly, this percutaneous treatment performed from the femoral vein consists in a transluminal angioplasty of the CTEPH lesion thanks to balloon dilatation catheter (*Part II, figure 1*). Several treatment sessions are necessary to obtain a complete treatment of the lesions (*figure 6, Supplementary files*) and to avoid complications, in particularly reperfusion pulmonary edema (*figure 7, Supplementary files*). Other complications of this procedure are hemoptysis, vascular injury, contrast-induced nephropathy, and death.

If the first report by *Feinstein et al.*, was limited by a high complication rate with 61% of reperfusion pulmonary edema (27% of them required mechanical ventilation) and 11% of peri-procedural death ⁽⁹²⁾, more recent studies have reported better outcomes. Indeed, several studies summarized in *table 5*, mostly from Japan, revealed multiple benefits of BPA with a lower complication rate. After a mean number of procedures, between 3 and 5 per patient, mean pulmonary artery pressure (mPAP) was normalized or significantly reduced, pulmonary vascular resistance was reduced from 30 to 60%, and 6-minute walk distance increased up to 90meters ^(93–100). Presently, peri-procedural death has been reduced to 0, and the complication rate to around 10% without poor outcome. BPA also improved right ventricular function ^(101–105), and respiratory function ^(106,107). Besides these encouraging results, it is important to notice that BPA was associated with a medical treatment in around 70% of all these studies, and no study have evaluated BPA versus medical treatment in a randomized control trial. The *Race* study (ClinicalTrials.gov identifier NCT02634203) is currently in progress to answer this question. Moreover, only one study reported the long-term effects of BPA with a five-year survival of 98.4% ⁽⁹⁹⁾, but this has to be confirmed by others and with bigger cohorts of patients.

Table 5: Overview of studies (including more than 50 patients) evaluating balloon pulmonary angioplasty

| Author, year | Kurzyna M, 2017 | Kriechbaum SD, 2017 | Olsson KM, 2017 | Ogawa A, 2017 | Aoki T, 2017 | Inami T, 2014 | Kimura M, 2016 | Ogo T, 2017 |
|---------------------------------------|-------------------------------|------------------------------|------------------------------|-------------------------------|------------------------------|--------------------------------|------------------------------|-------------------------------|
| Country | Poland | Germany | Germany | Japan | Japan | Japan | Japan | Japan |
| No. Study sites | 1 | 1 | 2 | 7 | 1 | 2 | 1 | 1 |
| Enrolment period | - | 2014-2017 | 2014- | 2004-2013 | 2009-2016 | 2009-2013 | 2012-2016 | 2011-2015 |
| No. Participants | 56 | 51 | 56 | 308 | 77 | 103 | 67 | 80 |
| Age, y | 58,6 ± 17,9 | 63,1 ± 11,5 | 65,0 ± 0,0 | 61,5 ± 12,5 | 65,0 ± 14,0 | 63,3 ± 14,3* | 62,0 ± 13,9 | 67,3 ± 13,6* |
| female, % | 50 | 28 | 61 | 79,9 | 82 | 76,7 | 68,7 | 73,7 |
| Evolution of mPAP, mmHg | 51 ± 11 to 36 ± 9 | 40 ± 12 to 33 ± 13 | 40 ± 12 to 33 ± 11 | 43 ± 11 to 23 ± 5 | 38 ± 10 to 23 ± 6 | 41 ± 10* to 22 ± 8* | 39 ± 11 to 20 ± 4 | 42 ± 11 to 25 ± 6 |
| Evolution of PVR, WU | 10,3 ± 3,7 to 5,9 ± 2,8 | 6,4 ± 2,7 to 5,0 ± 2,3 | 7,4 ± 3,6 to 5,5 ± 3,5 | 10,7 ± 5,6 to 3,6 ± 2,4 | 7,3 ± 3,2 to 3,7 ± 1,5 | 9,4 ± 5,4* to 3,0 ± 1,6* | 9,7 ± 6,8 to 3,4 ± 1,5 | 11,0 ± 5,3 to 5,1 ± 2,3 |
| Evolution of CI, L/min/m ² | 2,3 ± 0,6 to 2,5 ± 0,5 | 2,5 ± 0,6 to 2,5 ± 0,5 | 2,4 ± 0,6 to 2,5 ± 0,6 | 2,6 ± 0,8 to 2,9 ± 0,7 | 2,7 ± 0,7 to 2,3 ± 0,4 | 2,5 ± 0,6* to 2,9 ± 0,8* | - | 2,3 ± 0,6 to 2,6 ± 0,6 |
| Evolution of 6MWD, m | 306 ± 153 to 397 ± 123 | 375 ± 0 to 409 ± 0 | 358 ± 108 to 391 ± 108 | 318 ± 122 to 430 ± 109 | 380 ± 138 to 499 ± 132 | 357 ± 113* to 427 ± 121* | 322 ± 109 to 446 ± 104 | 372 ± 124 to 470 ± 99 |
| Evolution of NYHA III-IV, % | 97 to 29 | 96 to 12 | 85 to 25 | 81 to 4 | 28 to - | 87 to - | 85 to 0 | 96 to - |

Abbreviations: 6MWD=6-minute Walk Distance; CI=Cardiac Index, NYHA=New York Heart Association functional class; mPAP=mean Pulmonary Arterial Pressure; PVR=Pulmonary Vascular Resistance. Values are expressed in mean ± standard deviation.

*Mean and standard deviation values were computed according to Wan et al (BMC Med Res Methodol. 2014 Dec 19;14:135.) from median and interquartile range.

Prognosis

The prognosis of CTEPH differs greatly between patients, depending on the severity of their disease, comorbidities, and the therapeutic possibilities. In 2001 *Lewczuk J et al.* reported an unfavourable prognosis for CTEPH patients not eligible for PEA, with mortality around 40% at 1 year for those with medium Pulmonary artery pressure above 30mmHg ⁽¹⁰⁸⁾. These results are consistent with previous studies including both PAH and CTEPH patients, with a possibly worst prognosis for CTEPH patients ^(109–111). Most recent studies have reported a better prognosis. In an international prospective registry, the survival of CTEPH patients at one, two, and three years was 93%, 91%, and 89% respectively for patients who had undergone PEA and 88%, 70%, 79% respectively for those treated medically ⁽⁷⁴⁾. Prognosis was similar in other European registries ^(3,4).

Gap of evidence

Despite recent progress in the understanding and the management of CTEPH, some questions are still waiting for answers: (i) The real incidence of the diseases is still unknown, (ii) the place of each diagnostic tool (SPECT, V/Q scintigraphy, DECT, CTPA, cone-beam computed tomography) need further examination, (iii) the benefits of a systematic screening of CTEPH in patient with PE should be precise, (iv) the place of BPA in the treatment algorithm needs more evaluation especially with randomized controlled trials, (v) interest of a bridging medical treatment before and after PEA or BPA need to be evaluated.

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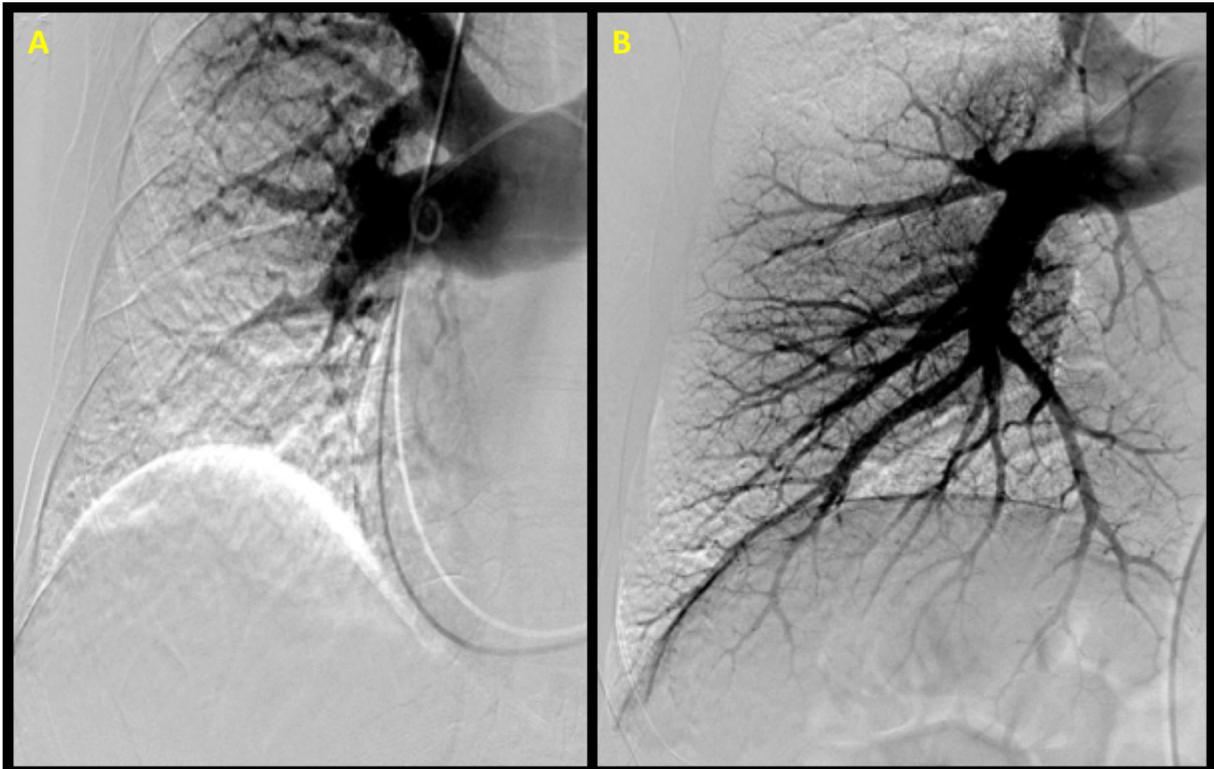
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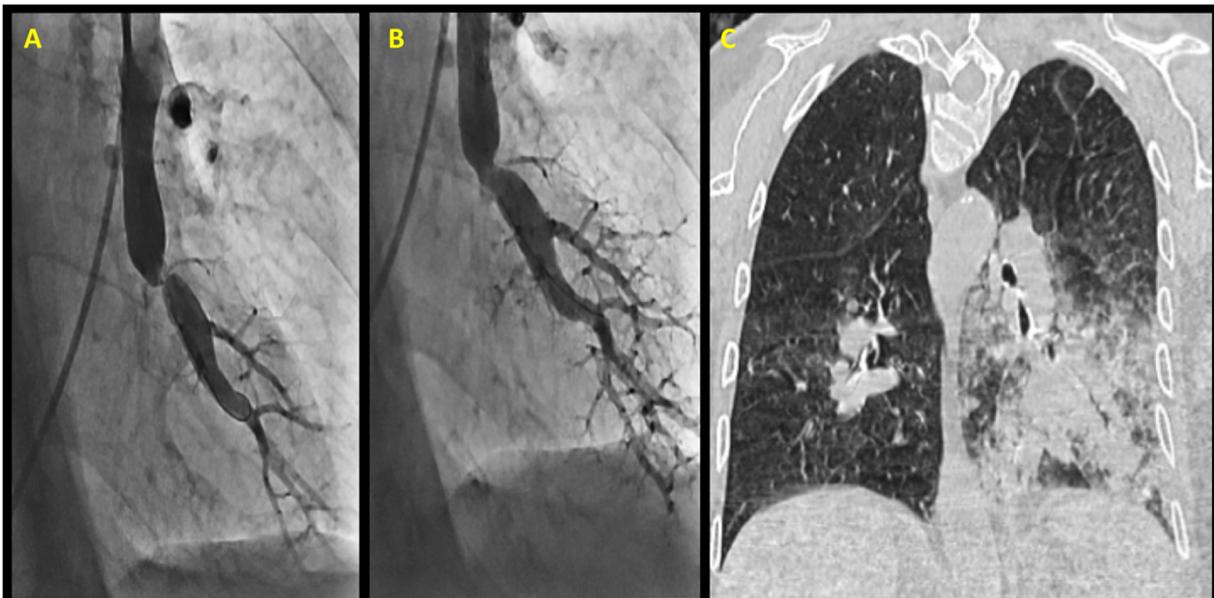
Supplementary files

Figure 6: Example of the treatment of the right inferior lobe by BPA



Digital subtraction angiography of the right inferior lobe before (A) and after (B) balloon pulmonary angioplasty.

Figure 7: Example of Reperfusion Pulmonary Edema following BPA



(A) Pre-BPA selective angiography showing a typical web lesion of the A9 branch of the left pulmonary artery (B) Post-BPA selective angiography confirming the good result of the transluminal angioplasty (C) Computed tomography performed after the procedure because of shortness of breath and desaturation confirming the presence of a severe reperfusion pulmonary edema of the left inferior lobe

PART II:
BALLOON PULMONARY ANGIOPLASTY FOR THE TREATMENT OF
CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION:
RESULTS FROM THE INITIAL GRENOBLE EXPERIENCE

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe progressive condition developing in 0.1 to 9.1% of patients within the first 2 years of symptomatic pulmonary embolism ^(1,2). It stems from persistent obstruction of proximal pulmonary arteries by residual thromboembolic material and consecutive vascular remodelling of non-occluded precapillary arteries ^(3,4). The natural course of CTEPH is characterized by elevated pulmonary vascular resistance (PVR) leading to progressive pulmonary arterial hypertension (PAH), right ventricular failure, and ultimately death ⁽⁵⁾.

Three treatment options are currently available, depending on the level of pulmonary artery obstruction and patient operability ^(1,6). Pulmonary endarterectomy (PEA) remains the first-line recommended, and potentially curative, treatment for patients with CTEPH amenable to surgery ⁽⁷⁾. Yet up to 40% of patients are not operable because of distal lesions that are technically inaccessible to surgery or the presence of severe comorbidities that preclude surgery ^(5,6). Additionally, PAH persist or recurs following surgery in 5 to 35% of patients ^(8,9). The efficacy of medical therapy with PAH-targeted drugs (including riociguat) in symptomatic patients with either inoperable CTEPH or residual or recurrent pulmonary hypertension following PEA is supported by evidence derived from randomized placebo-controlled trials ⁽¹⁰⁻¹²⁾.

Balloon pulmonary angioplasty (BPA) has emerged as an option for treating patients with technically inoperable CTEPH, residual pulmonary hypertension following PEA, or unfavourable expected risk-benefit ratio of PEA ^(6,7). Published in 2001 ⁽¹³⁾, the first case series of 18 inoperable CTEPH patients treated with BPA reported significant improvements in hemodynamics and exercise capacity, but at the cost of pulmonary reperfusion edema and periprocedural death in eleven and one patients, respectively. Since this pioneering study, the BPA technique has been refined and used extensively in Japan ⁽¹⁴⁾, and more recently adopted

by European centers ^(6,15). Yet, published data on BPA benefits and safety in CTEPH remain relatively imprecise and heterogeneous.

Our primary objective was to compare exercise capacity, biochemical markers, hemodynamic, and health-related quality of life at baseline and follow-up for CTEPH patients treated with BPA at a single center in France. Our secondary objective was to derive summary estimates for outcome measure improvement and procedure-related complication incidence following BPA in CTEPH, based on published primary studies.

Methods

Study design

We analyzed the original data from an ongoing prospective hospital-based registry of CTEPH patients who were treated with BPA at Grenoble University Hospital, France (NCT02844036). All patients provided written informed consent for participation and follow-up. The study protocol was approved by Institutional Review Board (Comité de Protection des Personnes Sud-Est V) and data processing was authorized by the French data protection authority (Commission nationale de l'informatique et des libertés). The funders played no role in study design, data collection, analysis, interpretation of the data, writing of the report, or in the decision to submit the paper for publication.

Patients

The present analysis included all consecutive patients who were referred for treatment with BPA by PAH regional centers in France, between January 2014 and September 2016. Patients were enrolled if they 1) had a definitive diagnosis of CTEPH, 2) were recused for PEA, and 3) were eligible for BPA. The final diagnosis of CTEPH complied with current ⁽⁷⁾, based on medical history, physical examination, ventilation/perfusion lung scan, computed tomography pulmonary angiography, right-sided heart catheterisation (RHC), and digital subtraction pulmonary angiography findings.

All patients were assessed for operability by a multidisciplinary team at the national reference center (Kremlin Bicêtre, Paris France). Patients were deemed ineligible for PEA because of thrombi localizations that were technically inaccessible to surgery, severe comorbidities that precluded surgery, residual or recurrent pulmonary hypertension following PEA, or patient refusal.

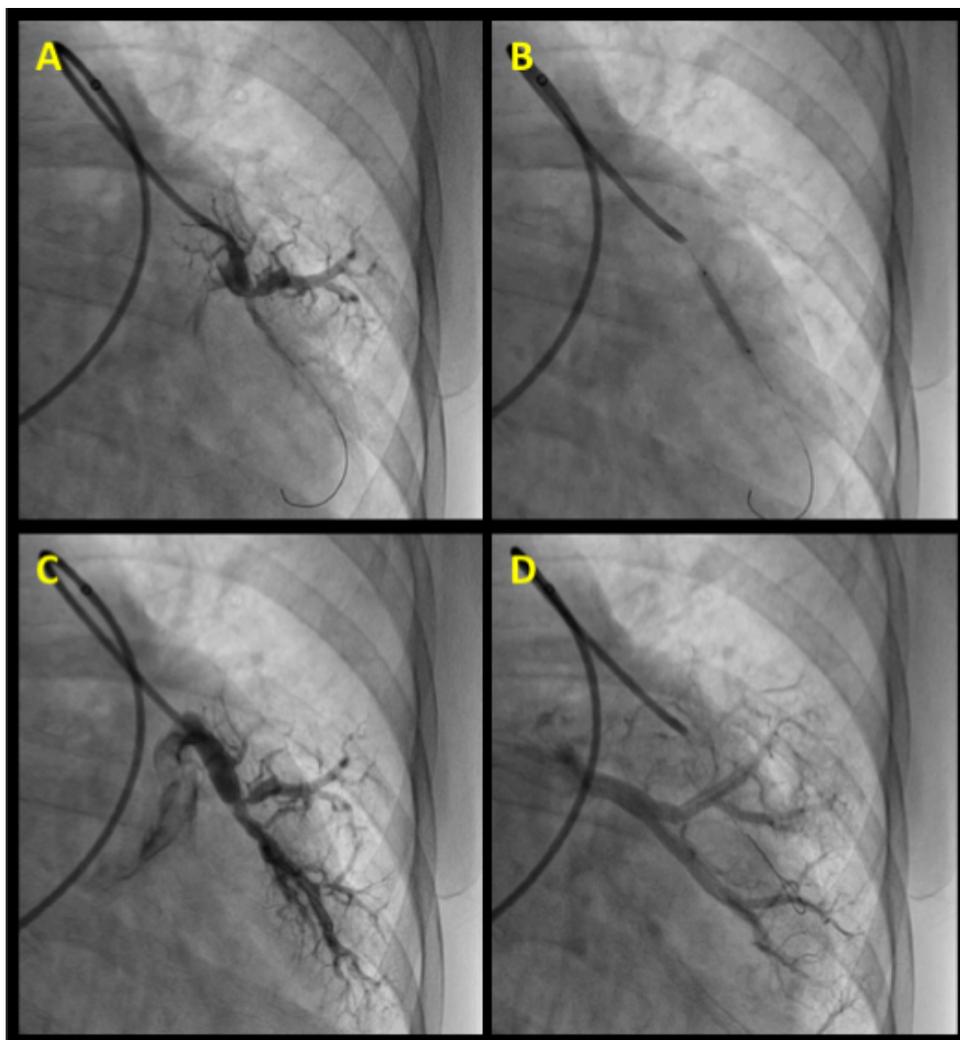
Inoperable patients were selected for BPA based on renal function with creatinine serum level <200 μmol/L or dialysis, ability of the patient to maintain in supine position during more than 1 hour and to maintain short apnoea, and the absence de comorbidities compromising short term survival.

Balloon pulmonary angioplasty

All patients were admitted in hospital the day before the procedure to check the absence of BPA contraindication, International Normalized Ratio (INR) control and proceed to standardized interventional preparation care. Oxygen saturation (SaO₂) and non-invasive systemic arterial pressure were carefully monitored during and 24h after the procedure and mean pulmonary arterial pressure was monitored during procedure. Therapy with vitamin K antagonist (VKA) was maintained before the procedure for an INR target around 2 and a bolus of unfractionned heparin of 20 UI/kg was injected at the beginning of the procedure. Mapping of the target lesions was elaborated before the procedure from V/Q scan, CTPA and DSA data. A 6F long sheath (Flexor, Cook Medical, Bloomington, USA) was introduced thanks to a 0.035 guidewire (Guideright, St Jude Medical, St Paul, USA) through the right femoral vein to the right atrium under local anaesthesia and short inhalation of fixed 50% nitrous oxide oxygen mixture when necessary. Then, a 6F guiding catheter (Judkins Right or Multipurpose Launcher, Medtronic, Minneapolis, MN, USA) was introduced into the long sheath, using a hydrophilic Terumo 0.035 wire to the pulmonary artery of interest and selected-angiography was performed during short apnoea. Target lesion was then crossed with a 0.014 hydrophilic wire (Pilot 150, Abbott Vascular, Santa Clara, CA, USA). Appropriate size of the balloon was determined by angiography. Balloon angioplasty was performed with percutaneous transluminal angioplasty balloon dilatation catheter from 2 to 7 mm of diameter and 20mm of length (from diameter 2 to 4mm: Euphora, Medtronic, Minneapolis, MN, USA; and from 5 to 7 mm: RX Muso, Terumo, Tokyo, Japan). Angiography was performed after each inflation to affirm the good result of the

angioplasty defined as an angiographic pulmonary flow grade 3, a good venous return flow and to eliminate a potential vascular injury (*figure 1*).

Figure 1: Major steps of a BPA procedure



(A) A 6-F guiding catheter is introduced to the pulmonary artery of interest and a 0,014 hydrophilic guidewire is introduced across the target lesion. (B) Balloon dilatation catheter is inflated on the site of the lesion. An angiographic control confirmed the good result of the transluminal angioplasty with obtaining of an angiographic pulmonary flow grade 3 (C) and a good venous return (D).

At the first session, BPA was performed more cautiously when PVR was high to avoid the risk of reperfusion pulmonary edema, in accordance with the *Pulmonary Edema Predicting Scoring Index* (PEPSI) ⁽¹⁶⁾. Only one lobe vessel was then treated and with balloon size less than 80% of the arterial size. Procedure was prematurely interrupted in case/because of

haemoptysis or oxygen desaturation >10%. All patient had clinical and SaO₂ monitored overnight and underwent a chest x-ray after the procedure.

As patient came from the whole country, treatment was most of the time performed in a stage-by-stage manner with 2 sessions in a week separated by a minimum of 2 days to avoid multiple hospitalizations. When procedures were uncomplicated, discharge from hospital occurred 24h after the last procedure. Two to eight weeks separates each period of 2 sessions.

The treatment goal was to obtain NYHA class I or II with mPAP<35mmHg without major angiographic residual occlusion.

Measurements

All patients underwent comprehensive assessment including World Health Organization (WHO) functional class, 6-min walk distance (6MWD), health-related quality of life, serum levels of creatinine and N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), and RHC, at baseline (i.e., prior to the first BPA procedure) and 6 to 12 months after the last BPA procedure. Health-related quality of life was evaluated using the cross-cultural adaptation of the Short form-36 version 2 Health Survey (SF-36) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) into French.

The SF-36 is a generic health survey that is comprised of 36 items covering eight dimensions (i.e., physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions) and yielding two (i.e., physical and mental) summary scores ⁽¹⁷⁾. Each score ranges from 0 to 100, with higher values denoting better quality of life. SF-36 scoring was performed using a certified software (OPTUM, Eden Prairie, MN, USA).

The MLHFQ is a 21-item questionnaire designed to measure the adverse effects of heart failure on patient quality of life during the past 4 weeks. The overall score ranges from 0 to

105, with lower values denoting lower effect of heart failure on the quality of life ⁽¹⁸⁾. A 5-point improvement in MLHFQ score is considered clinically relevant ⁽¹⁹⁾.

RHC was performed with a 6-Fr Swan-Ganz catheter in supine position and evaluated mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), pulmonary vascular resistance (PVR), right atrial pressure (RAP), cardiac output (CO), and cardiac index (CI). CO was determined using the thermodilution method and CI was computed by dividing CO by body surface area. PVR was computed by subtracting PAWP from mPAP and dividing by CO.

BPA procedure-related complications

Complications were prospectively recorded and adjudicated by two interventional cardiologists experienced in management of CTEPH. BPA procedure-related complications were defined consistently with previous studies ⁽²⁰⁾ and included haemoptysis, pulmonary oedema, use of non-invasive positive pressure ventilation, oral intubation with mechanical ventilation, and peri-procedural death.

Haemoptysis during or on the day of the procedure was defined as procedure-related ⁽²⁰⁾. Haemoptysis requiring embolization were recorded separately. Pulmonary oedema was defined as X-ray opacity in the lung segment treated with BPA on the day or next day of the procedure, which induced a prolongation of the hospitalization stay. Non-invasive positive pressure ventilation or oral intubation with mechanical ventilation for haemoptysis or pulmonary oedema were performed at the discretion of physicians.

Peri-procedural death was defined as death that occurred within 30 days of the procedure ⁽²⁰⁾. Other complications included non-specific adverse events that occurred on the day or next day of the procedure.

Radiation exposure

Radiation exposure measurement was recovered automatically with Radiation Dose Monitor (Medsquare, Paris, France). Dose area product (DAP), cumulative air Kerma and Fluoroscopy time were reported at each session. Dose-area product is a measure of the total x-ray energy leaving the x-ray tube, estimated in gray–square centimeters (Gy.cm²). It is used to evaluate the risk of stochastic hazard of the procedure. Effective-dose (ED), expressed in millisievert (mSv) was calculated according to the following formula: ED (mSv) = DAP (Gy.cm²) × 0.2, as previously described ⁽²¹⁾. Cumulative air kerma corresponds of the air kerma accumulated on the reference point, which is situated on the central axis of the x-ray beam, 15cm under the isocenter on the x-ray tube side. It's an indicator of the likelihood of skin injury and it is estimated in milligray (mGy).

Systematic review

The inclusion criteria and analysis methods for our systematic review were prespecified and registered with PROSPERO. Briefly, prospective cohort studies and retrospective case series were eligible if they included 10 or more consecutive patients treated with BPA for CTEPH. Primary studies were identified by searching MEDLINE via PubMed (from 2000 to March 2018). The search strategy was developed by a member (Nicolas Piliero) from the project team and used both standardized medical subject heading (MeSH) and text words. The search concepts included BPA and CTEPH. The electronic search was supplemented by scanning the reference lists of original articles identified as being potentially relevant and those of the previously published reviews for additional studies. One review author (Nicolas Piliero) screened the titles and abstracts, where available, for all records identified by the search strategy. Full-text articles of records identified as being potentially relevant were independently assessed by two review authors (Nicolas Piliero and José Labarère) for inclusion. Articles published in English or French languages were included in the review. In case of duplicate

publications or records with partially redundant data, the most recent report was included. Using a data abstraction form, the two review authors independently extracted qualitative and quantitative information for each primary study.

Statistical analysis

Categorical variables were reported as numbers and percentages and continuous variables as means and standard deviations or medians and ranges or interquartile ranges ([IQR], 25th to 75th percentiles), when appropriate. Follow-up and baseline continuous outcome measures were compared using the Student t-test for paired samples. Point estimates for mean difference in outcome measure (i.e., follow-up minus baseline measures) were reported along with 95% confidence intervals (95% CI). We adjusted the significance probability for multiple comparisons using the Bonferroni method. Follow-up and baseline categorical variables were compared using the Mac Nemar test for paired samples.

Meta-analysis. Means and standard deviations were computed according to Wan et al (22) for primary studies reporting medians and interquartile ranges. Mean difference was computed as mean follow-up measure minus mean baseline measure. Standard deviation (SD) for the difference was calculated as:

$$SD_{\text{difference}} = \sqrt{SD_{\text{follow-up}}^2 + SD_{\text{baseline}}^2 - 2 \times r \times SD_{\text{follow-up}} \times SD_{\text{baseline}}}$$

where r is the correlation coefficient between baseline and follow-up measure. When information on correlation was not available from primary study reports, we assumed a correlation coefficient equal to 0.5 (12). Point estimates from each primary study were combined using a DerSimonian and Laird's random-effects meta-analysis model for combining weighted mean differences in continuous variables. Between-study heterogeneity was evaluated graphically by examining forest plots and statistically by using the I^2 inconsistency index. The I^2 index provides an estimate of the percentage of total variance across studies due to

heterogeneity rather than chance. An I^2 index of 0% indicates no evidence of heterogeneity and higher values reflect increasing heterogeneity ⁽²³⁾.

Two-sided p -values of less than 0.05 were considered statistically significant. All analyses were performed using Stata SE 14 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristic

Between January 2014 and September 2016, 53 consecutive patients were referred to hospital for treatment with BPA. All of them underwent BPA procedures and were enrolled in the present study. The mean age at baseline was 71 ± 12 years old (range, 37 to 88). 22 patients (41,5%) were older than 75 years old. Baseline characteristics are summarized in [Table 1](#). 38 patients (71,7%) were treated with a specific PH treatment, 21 (39,6%) with an oral monotherapy and 16 (30,2%) with an oral dual therapy. One patient had subcutaneous Treprostinil tritherapy.

BPA procedures

A total of 197 sessions were performed to treat the 53 patients. The mean number of sessions per patient was 3.7 (range 2 – 7) with a BPA treatment duration of $72,5 \pm 68,8$ days. The mean number of vessels dilated per session was 3.5 (range 1-8) and the mean number of vessels dilated/patient was 9.0 (range 2-16). Branches of the inferior lobes were the most treated segments in the both lungs (Segments A8, A9 A10 treated in 62,3, 84,9, and 83% of patients respectively for the left lung; and 60,4, 84,9 and 90,6% respectively for the right lung).

Outcomes of BPA

The average follow-up period between the last procedure and evaluation by RHC was 303 ± 152 days. Major outcomes are resume in [figure 2](#). Five patients declined follow-up assessment visits because of age, poor global health and/or comorbidities. In the 48 others patient, NYHA functional class was improved in most of patient with a percentage of patient in class III-IV reduced from 83,3% to 12,5% ($p < 0,001$). Values for 6MWD and NT-proBNP were not available for eight and two additional patients, respectively.

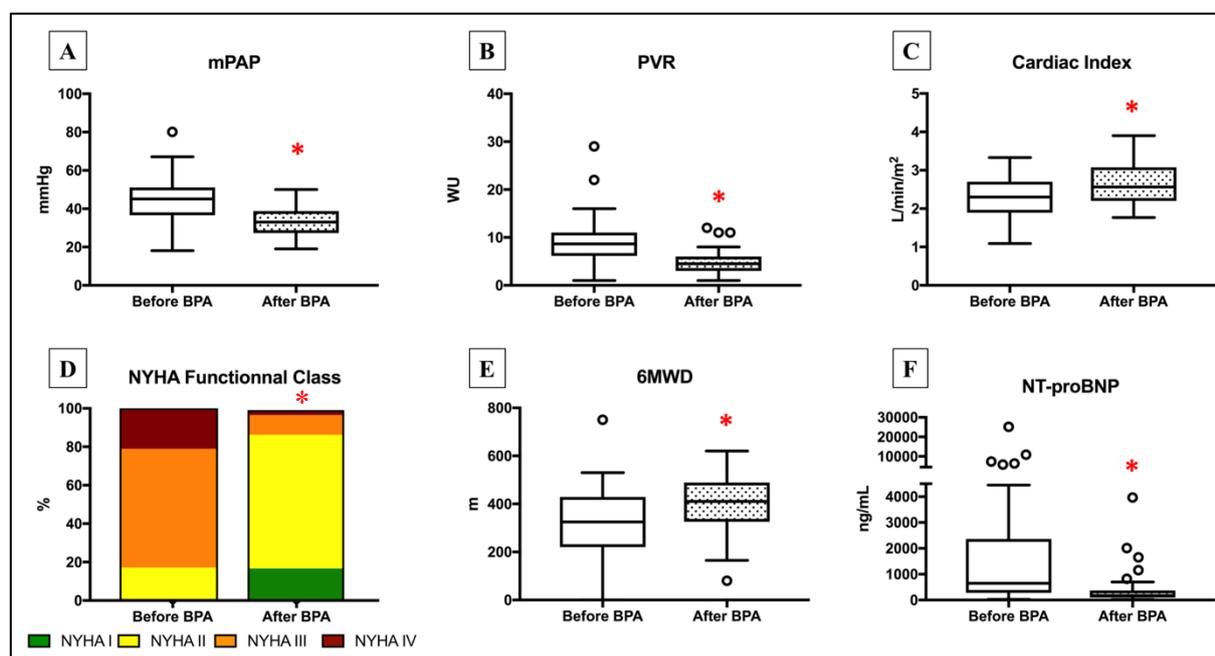
Table 1: baseline characteristics

| Characteristics | Patients (N=53) | |
|--|-----------------|--------------|
| Female gender, n (%) | 28 | (52.8) |
| Age, y, mean (SD) | 70.9 | (12.3) |
| Body mass index, kg/m^2 , mean (SD) | 25.2 | (3.9) |
| Indication for BPA, n (%) | | |
| Inoperable distal lesion | 34 | (64.2) |
| Severe comorbid conditions | 14 | (26.4) |
| Persisting CTEPH following PEA | 5 | (9.4) |
| Total of procedures per patient, mean (SD) | 3.7 | (1.4) |
| Functional parameters | | |
| NYHA I/II/III/IV, n (%) | 0/9/33/11 | (0/17/62/21) |
| 6MWD, m, mean (SD) | 315,5 | (171,4) |
| Hemodynamic data | | |
| PVR, <i>WU</i> | 9,0 | (4,7) |
| mPAP, <i>mmHg</i> | 44,8 | (11,5) |
| Cardiac index, <i>L/min/m²</i> | 2,3 | (0,5) |
| RAP, <i>mmHg</i> | 8,0 | (3,2) |
| NT-proBNP, <i>pg/mL</i> , mean (SD) | 2138,4 | (3885,5) |
| Medications, n(%) | | |
| Home therapy with oxygen | 20 | (37,7) |
| VKA therapy | 53 | (100) |
| Diuretics | 34 | (64,2) |
| PDE5i therapy | 16 | (30,2) |
| ERA therapy | 22 | (41,5) |
| Prostacyclin therapy | 1 | (1,9) |
| sGC therapy | 18 | (34,0) |
| Any therapy with pulmonary vasodilator, n(%) | | |
| Monotherapy | 21 | (39,6) |
| Bitherapy | 16 | (30,2) |
| Tritherapy | 1 | (1,9) |

Abbreviations: CI = confidence interval; BNP = brain natriuretic peptide; PDE5i = phosphodiesterase type 5 inhibitor; ERA = endothelin receptor antagonist; sGC = activator of soluble guanylate cyclase; SD = standard deviation, VKA= Vitamine K Antagonist. * Values were missing for PVR (n=1), 6MWD (n=4), NT-proBNP (n=2).

Compared with baseline values, 6MWD (mean difference, 94 m, 95% CI, 56 to 131) and NT-proBNP level ($1872,7 \pm 3898,9$ to $405,7 \pm 675,8$ pg/mL; $p=0,01$) significantly improved following BPA treatment. Hemodynamic parameters, including mPAP (-11 mmHg, 95% CI, -14 to -7.7), PVR (-3.8 WU, 95% CI, -5.1 to -2.6), cardiac output ($0.6 \text{ L} \cdot \text{min}^{-1}$, 95% CI, 0.3 to 1.0), and cardiac index ($0.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, 95% CI, 0.1 to 0.5) improved while RAP remained unchanged (-1.0 mmHg, 95% CI, -2.1 to 0.1). However, $\text{mPAP} \geq 25 \text{ mmHg}$ and $\text{PVR} \geq 3 \text{ WU}$ were observed in 42 (87,5%) and 41 (85,4%) patients, respectively

Figure 2: Major outcomes of BPA



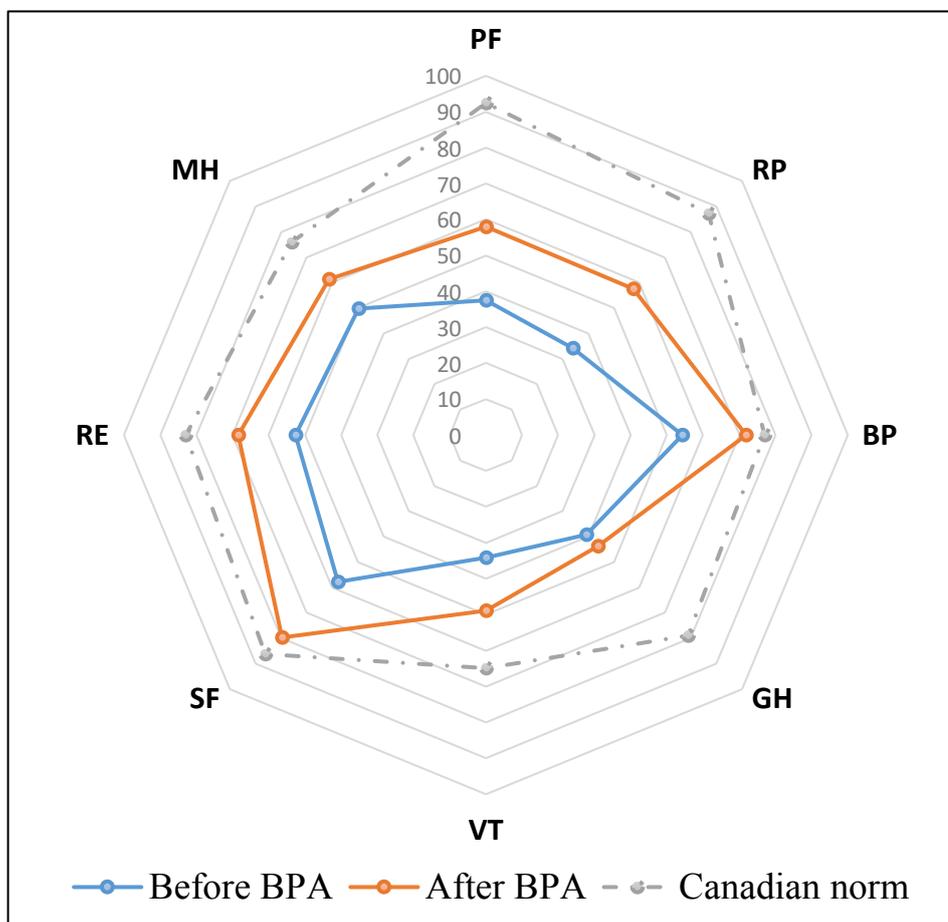
Changes in Hemodynamic, functional status, exercise capacity and NTproBNP serum level before BPA procedure and at follow-up ("After BPA"). (A) mPAP=Mean pulmonary arterial pressure; (B) PVR= Pulmonary vascular resistance; (C) Cardiac index; (D) NYHA functional class; (E) 6MWD= 6-minut walk distance; (F) NT-proBNP serum level. Values were missing for PVR (n=1 pre-BPA, n=6 post-BPA), mPAP (n=5 post-BPA), cardiac index (n=5 post-BPA), 6MWD (n=4 pre-BPA, n=13 post-BPA), NT-proBNP (n=2 pre-BPA, n=7 post-BPA).

Bars depict medians, **Boxes** depict interquartile ranges, **whiskers** depict ranges excluding statistical outliers (**Circles**) (Tukey method). * $p < 0,01$ versus "before BPA"

29 unselected patients of the 53 patients completed HRQOL forms. Both physical and mental scale summary and the seven following components of the SF-36v2 were improved at follow-up, and above or near to the MID: physical functioning, role physical, bodily pain, vitality, social functioning, mental health and role emotional (figure 3). Physical summary score,

emotional summary score and total summary score of the MLHFQ score were also better at follow-up ([table 2](#)).

Figure 3: Health-Related Quality of life evaluated by SF36v2



Abbreviations: PF=Physical Functioning; RP=Role-Physical; BP=Bodily Pain; GH=General Health; VT=Vitality; SF=Social Functioning; RE=Role-Emotional; MH=Mental Health. Higher scores indicate better perceived health status.

BPA also allowed to reduce diuretic utilisation from 31 patients (62%) to 20 patients (40%) but these results didn't reach the statistical significance after Bonferroni adjustment. The percentages of patients requiring PAH-targeted drugs, or home oxygen therapy did not differ between baseline and follow-up assessments. Paired-comparisons of concomitant treatments are available in [supplementary files, Table 5](#).

Table 2: Paired comparisons of Health-related quality of life outcome

| Outcomes* | N | Pre-BPA procedure | | Post-BPA procedure | | Mean difference (95% CI) | P [†] | |
|-------------------------|----|-------------------|--------|--------------------|--------|--------------------------|----------------|--------|
| | | Mean | (SD) | Mean | (SD) | | | |
| SF36v2 [†] | | | | | | | | |
| Physical summary score | 29 | 37.2 | (7.9) | 44.0 | (8.3) | -6.7 | (-9.8 – -3.7) | .0001 |
| Mental summary score | 29 | 39.6 | (12.2) | 45.8 | (10.1) | -6.2 | (-11.2 – -1.3) | .02 |
| MLHFQ | | | | | | | | |
| Physical summary score | 29 | 21.9 | (9.9) | 14.5 | (9.5) | 7.4 | (4.6 – 10.3) | <.0001 |
| Emotional summary score | 29 | 9.9 | (7.1) | 5.7 | (5.4) | 4.3 | (1.7 – 6.9) | .002 |
| Total summary score | 29 | 43.4 | (21.7) | 26.3 | (18.8) | 17.1 | (10.1 – 24.0) | <.0001 |

* Values were missing for SF36v2 (n=19 pre-BPA, n=24 post-BPA), MLHFQ (n=19 pre-BPA, n=10 post-BPA)

[†] z-score for Physical summary score and Mental summary score and scores 0 to 100 for 8 different dimensions.

Complications of BPA

Complication rate of BPA was relatively low and are resume *in table 3*. During the 197 sessions, haemoptysis occurred 13 times (6.6%), and none required embolization. Three of them were secondary to a guide-wire perforation and were treated with a prolonged low-pressure inflation of the balloon in the proximal part of the artery to stop the flow. Reperfusion pulmonary edema occurred for 6 procedures (3,0%) and 6 patients (11,3%). 3 patients required non-invasive positive pressure ventilation for the treatment of this reperfusion edema. Others have favourable outcome with oxygen and diuretics. No patient required mechanical ventilation.

Those complications induced prolongation of the hospitalization from 2 to 8 days. We deplore no death during or in the month after procedure. No acute renal injury was induced by BPA. Nevertheless, in a patient-based analysis, 30,2% of patients experienced a complication during the whole treatment.

Table 3: Cumulative incidence of procedure-related complications.

| Procedure-related complication, <i>n</i> (%) | Session-based analysis | Patient-based analysis |
|--|------------------------|------------------------|
| | 197 sessions | 53 patients |
| Hemoptysis | 13 (6.6) | 10 (18.9) |
| Hemoptysis requiring embolization | 0 (0.0) | 0 (0.0) |
| Pulmonary edema | 6 (3.0) | 6 (11.3) |
| Non-invasive positive pressure ventilation | 3 (1.5) | 3 (5.7) |
| Oral intubation with mechanical ventilation | 0 (0.0) | 0 (0.0) |
| Acute renal injury | 0 (0.0) | 0 (0.0) |
| Other procedure-related complication | 4 (2.0) | 3 (5.7) |
| Any procedure-related complication | | 16 (30.2) |
| Peri-procedural death | | 0 (0.0) |

X-ray exposure

Radiation induced by BPA was substantial and is resume in [table 4](#). The median Dose Area Product per session was 10115 (Interquartile range (IQR)=6523-13779) cGy.cm² with a range between 467 and 65828cGy.cm². For the whole treatment, it corresponds to a median dose area product of 33926cGy.cm² (IQR=21714-56192) per patient with a range between between 11854 and 134676cGy.cm² per patient. Cumulative Air Kerma and fluoroscopy time were also important. No cutaneous injury or neoplasia was report during the treatment and the follow-up.

Table 4: X-ray exposure

| X-ray exposure * | No. sessions | Median | IQR | [min; Max] |
|---|--------------|--------|---------------|----------------|
| Dose area product per session, cGy.cm ² | 193 | 10115 | (6523-13779) | [467-65828] |
| Effective dose mSv | 193 | 20 | (13-28) | [1-132] |
| Cumulative air kerma per session, mGy | 182 | 900 | (556-1331) | [73-11408] |
| Fluoroscopy time per session, min | 193 | 41 | (31-53) | [2-92] |
| | No. patients | | | |
| Cumulative dose area product per patient, cGy.cm ² | 50 | 33926 | (21714-56192) | [11854-134676] |
| Cumulative effective dose, mSv | 50 | 68 | (43-112) | [24-269] |
| Cumulative air kerma per patient, mGy | 43 | 2964 | (2031-4612) | [1017-19106] |
| Cumulative fluoroscopy time per patient, min | 50 | 144 | (112-201) | [44-359] |

Abbreviations: IQR = interquartile range.

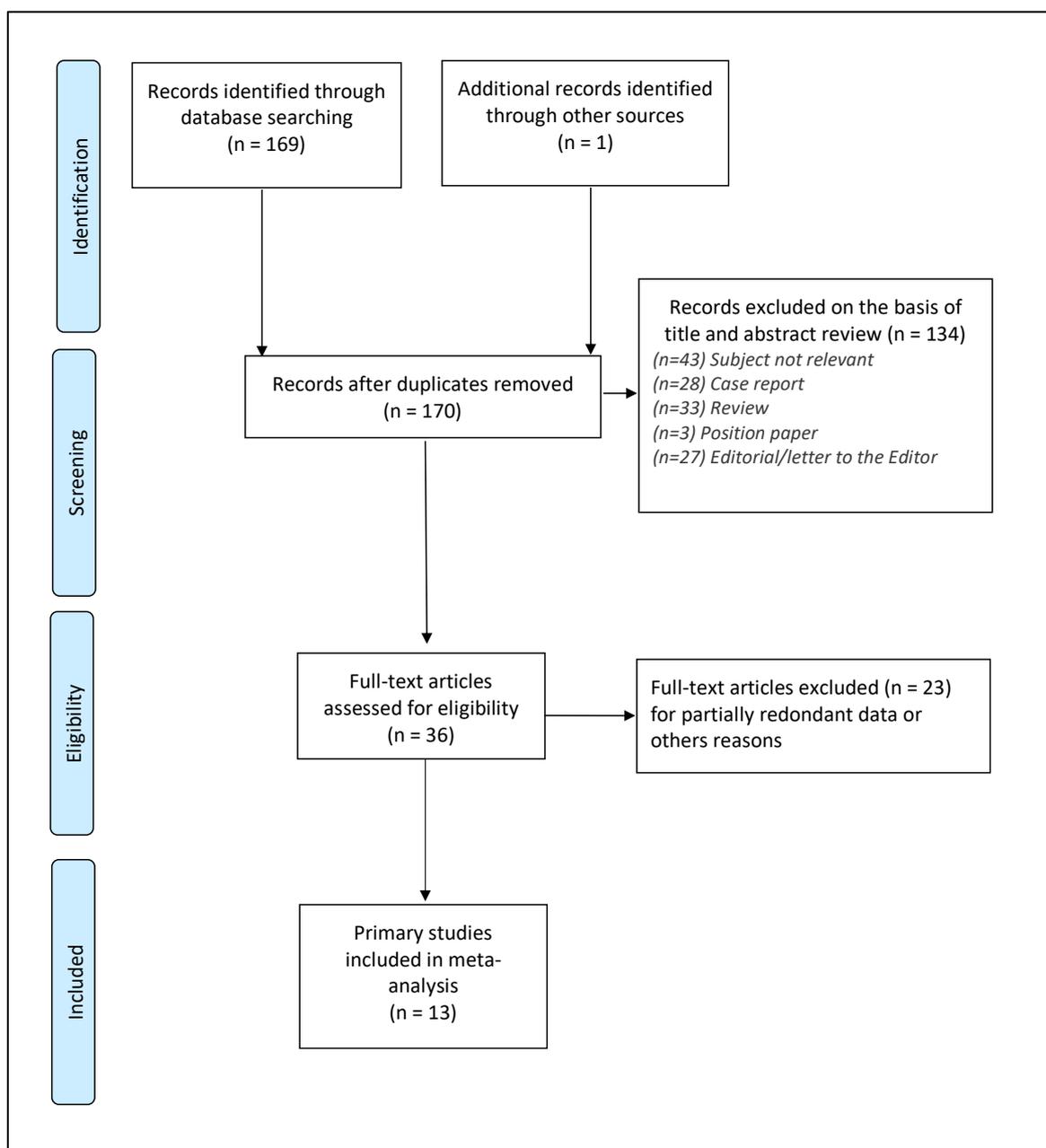
** Values were missing for dose area product per session (n=4), effective dose per session (n=4), cumulative air kerma per session (n=15), fluoroscopy time per session (n=4), cumulative dose area product per patient (n=3), cumulative air kerma per patient (n=10) and cumulative fluoroscopy time per patient (n=3)*

Systematic review with meta-analysis

A total of 169 records were identified through database searching (*figure 4*). The titles and abstracts for 36 records were identified as being potentially relevant and full-text articles were retrieved for more thorough review. After excluding 23 records based on full-text articles, our systematic review included 13 primary studies (including the present one) totaling 613 CTEPH patients who were treated with BPA. All, but one ⁽²⁴⁾, studies were conducted at single centers located in Japan (n=7), Europe (n=4), Korea (n=1), and the US (n=1) (*supplementary files, Table 6*). Primary studies recruited a median number of 51 patients (range, 15 to 103), with enrollment periods extending from 1994 to 2017. The mean age for all patients was 64 years and the median prevalence of female gender was 69% (range, 47 to 84).

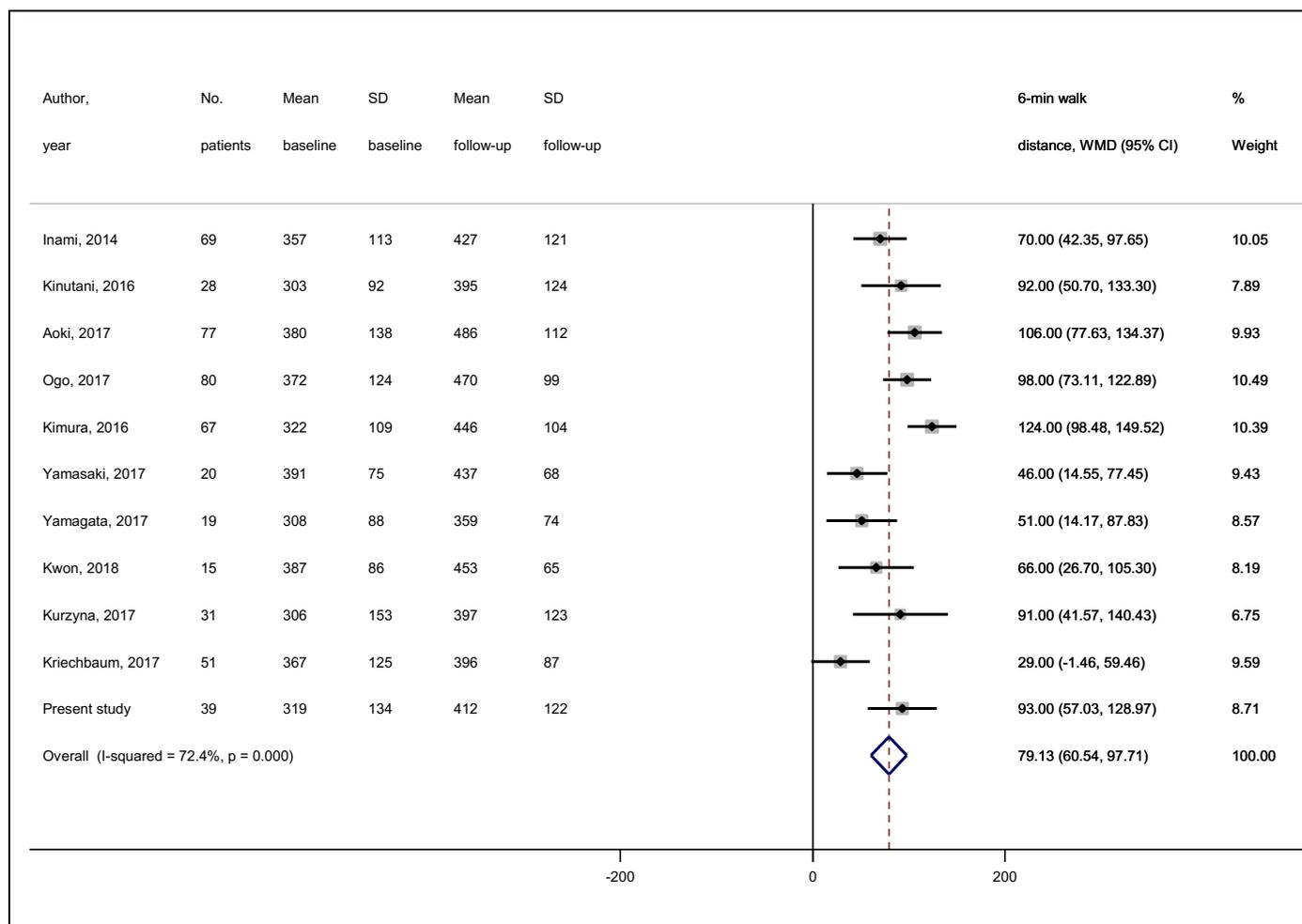
Using a random effect model, the mean increase estimate in 6MWD was 79 m (95% CI, 61 to 98), from 348 m at baseline to 427 m at follow-up for 496 patients (*figure 5*). Mean improvement estimates in hemodynamics were -14 mmHg (95% CI, -16 to -12) for mPAP, decreasing from 41 mmHg at baseline to 27 mmHg at follow-up in 563 patients (*figure 6*), and -4.0 WU (95% CI, -5.0 to -3.1) for PVR, decreasing from 8.4 WU at baseline to 4.3 WU at follow-up in 544 patients (*figure 7*). Cardiac index mean value did not vary significantly ($0.1 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, 95% CI, 0.0 to 0.3), between baseline and follow-up (2.5 versus $2.6 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, $P=.06$) in nine studies accruing 423 patients (*figure 8*). Of notice, significant heterogeneity between Japanese and European studies was observed for improvement in 6MWD (85 m, 95% CI, 63 to 107, versus 69 m, 95% CI, 23 to 115, P for interaction =.03), mPAP (-16, 95% CI, -19 to -14, versus -11, 95% CI, -14 to -7, P for interaction <.001) and PVR (-4.7, 95% CI, -5.8 to -3.6, versus -3.1, 95% CI, -4.6 to -1.6, P for interaction <.001).

Figure 4: Prisma-style flow chart of the meta-analysis



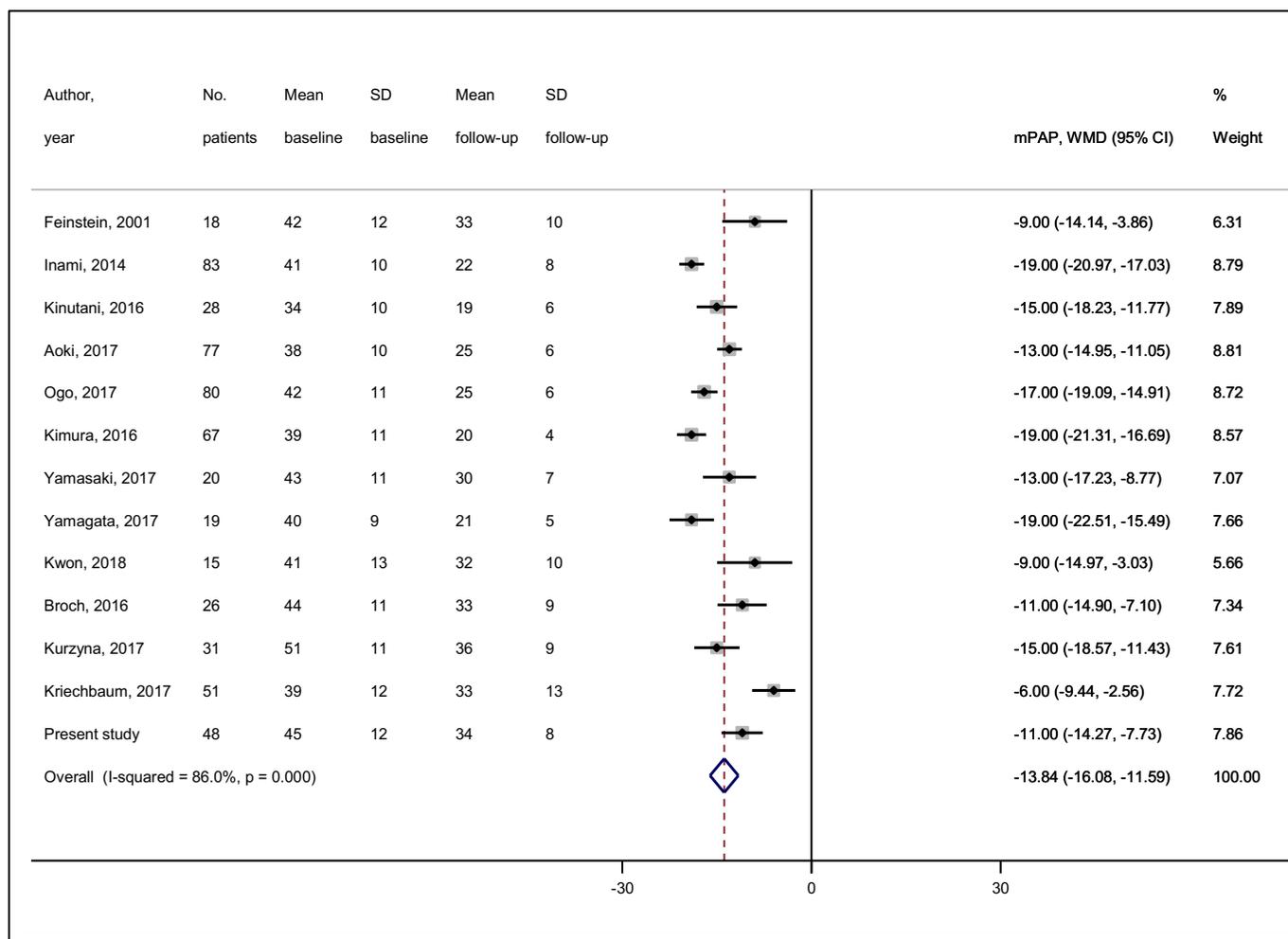
Overall, five periprocedural deaths occurred in 596 patients (0.8%, 95% CI, 0.3 to 1.9). Summary estimates of procedure-related complication incidence were, 8.5% (95% CI, 4.8 to 12), and 8.9% (95% CI, 5.6 to 12) for, pulmonary edema, and hemoptysis, in eight to 10 studies totaling 1294 to 1964 BPA sessions, respectively (*supplementary files, Figure 9 and 10*). Yet, substantial between-study heterogeneity was observed in procedure-related complication incidence, which was not explained by regional variations.

Figure 5: Random-effect summary estimate for difference in 6-min walk distance at baseline and follow-up.



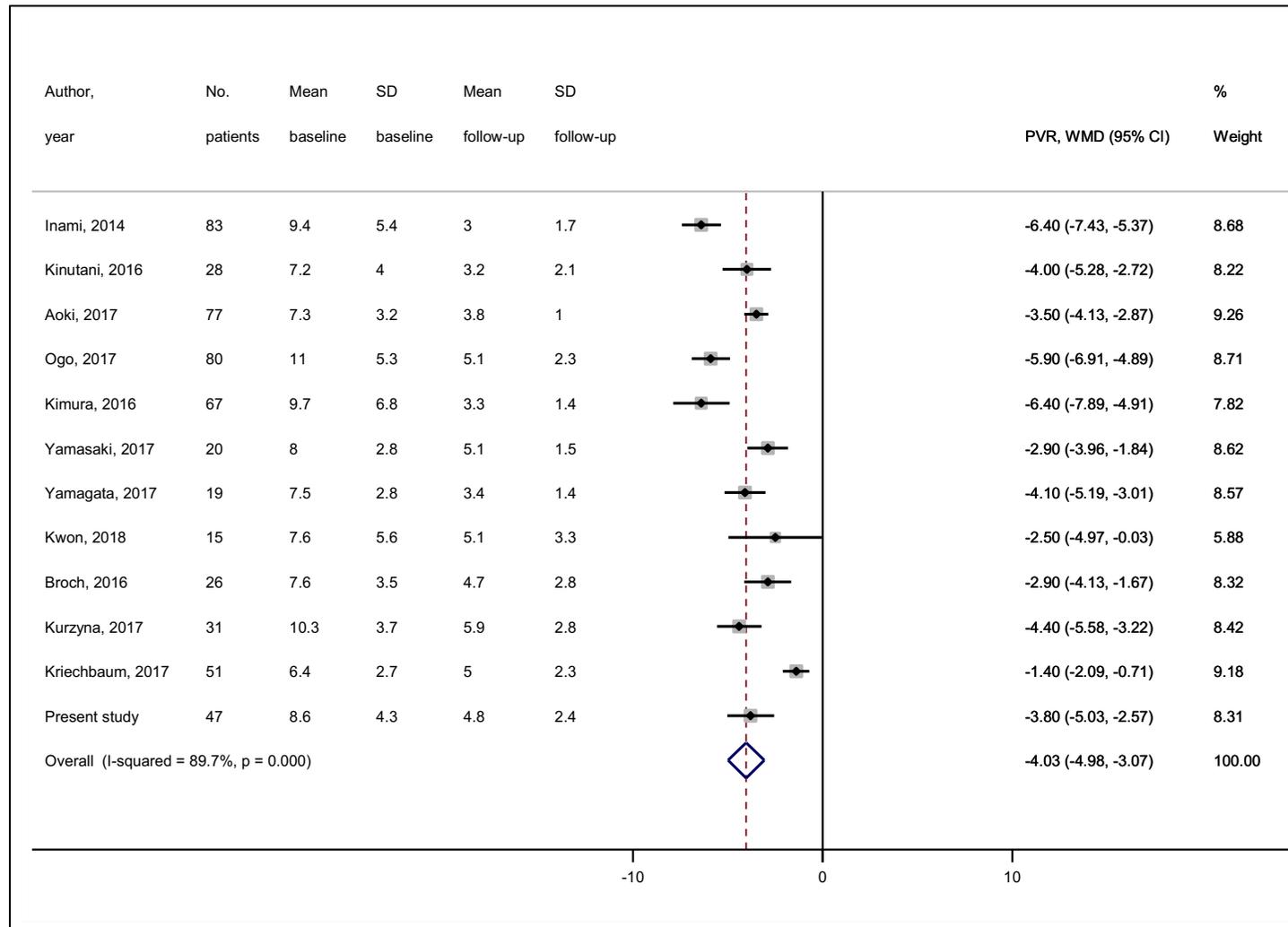
Abbreviations: CI = confidence interval; SD = standard deviation; WMD = weighted mean difference.

Figure 6: Random-effect summary estimate for difference in mean pulmonary arterial pressure at baseline and follow-up.



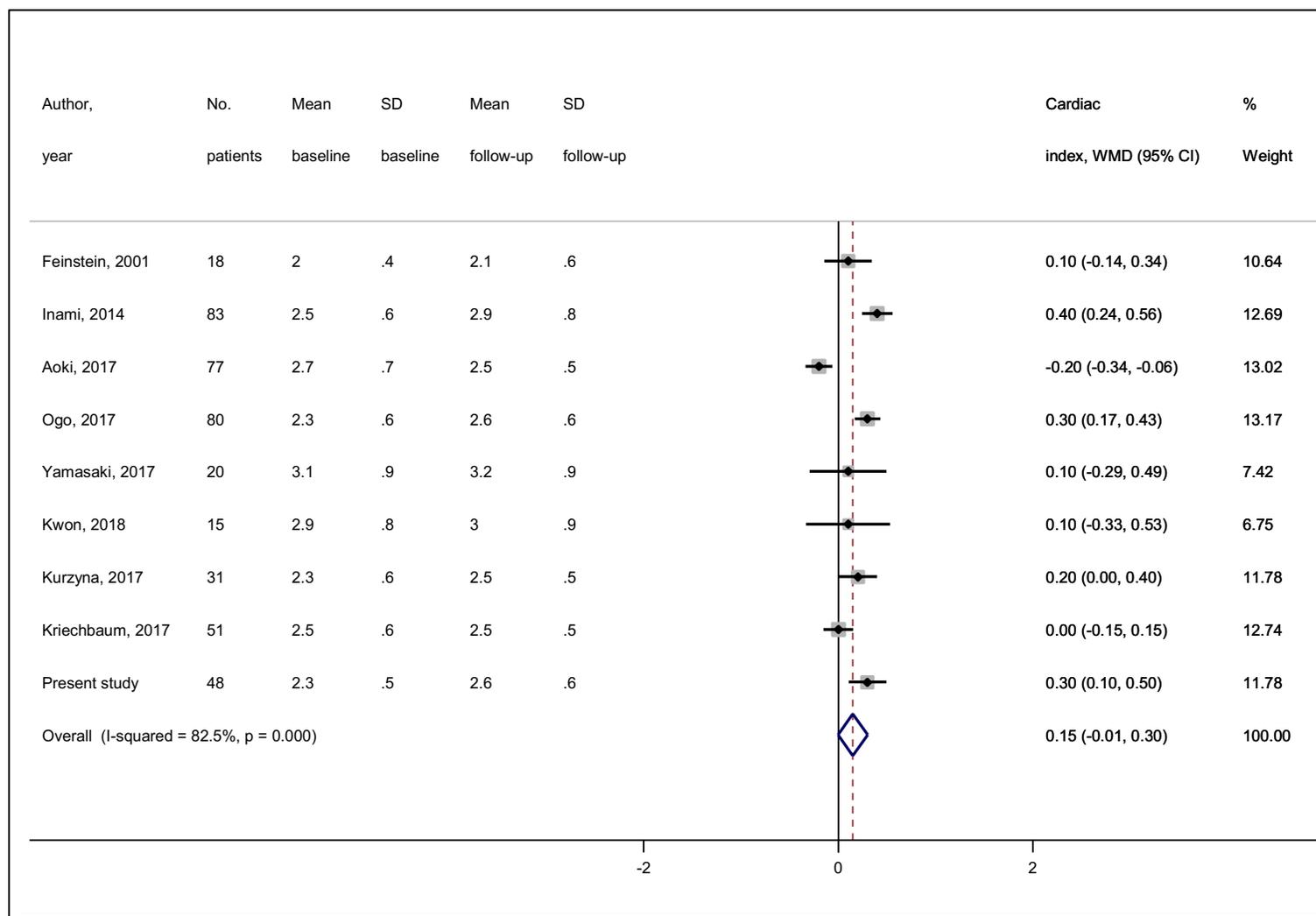
Abbreviations: CI = confidence interval; mPAP = mean pulmonary arterial pressure; SD = standard deviation; WMD = weighted mean difference.

Figure 7: Random-effect summary estimate for difference in pulmonary vascular resistance at baseline and follow-up.



Abbreviations: CI = confidence interval; PVR = pulmonary vascular resistance; SD = standard deviation; WMD = weighted mean difference.

Figure 8: Random-effect summary estimate for difference in cardiac index at baseline and follow-up



Abbreviations: CI = confidence interval; SD = standard deviation; WMD = weighted mean difference

Discussion

The key points that we highlight in this study are the following: (i) confirmation of the improvement of hemodynamic and functional status of patient who underwent BPA; (ii) feasibility of BPA in unselected patient, independently of age and comorbidity; (iii) benefits of BPA on HRQOL; (iv) safety of BPA with absence of major complications and without peri-procedural death; (v) special caution needed concerning radiation induced by BPA.

Benefits of BPA

Our study confirms the benefits and the safety of BPA for the treatment of CTEPH in patients not eligible for a PEA. Indeed, BPA allowed an average reduction of mPAP from 45mmHg to 34 mmHg, an average reduction of PVR from 8,6 to 4.8 UW, and an average elevation of cardiac index from 2.3 L/min/m² to 2.6L/min/m². These results are in accordance with previous study who showed a reduction of PVR from 30 to 50% corresponding to a mean reduction estimates in PVR of -4.0 WU (95% CI, -5.0 to -3.1) in our meta-analysis ([figure 7](#)). Mean PAP at follow-up is nevertheless a little higher than some recent studies where mPAP were normalized at the end of the treatment ([20,24–26](#)). We also observed in our meta-analysis a significant heterogeneity between Japanese and European studies for improvement in mPAP and PVR. These two differences might be explained by several factors. First of all, our experience concern prevalent patients with old disease and remodelled arteries from many years. Our feeling is that new lesions are easier to cross through and reverse remodelling is also easier to obtain in that case. This point of view need further investigations to be demonstrated. Secondely, regional variations in referral practices and patient selection for BPA may explain differing hemodynamics outcomes ([15](#)). Indeed, the localization and type of vessel lesion treatable by PEA and BPA is a subjective assessment ([6](#)). Thirdly, this difference could be also explained by the age of our population 10 years older than Japanese ([14](#)) or European recent

series (15,27–30) . Regarding this older age, the therapeutic goal was more focus on functional status than complete normalization of hemodynamic. Finally, we also think that the Japanese experience is much more efficient. Indeed, all studies, which showed a normalization of mPAP, are done in Japan, in centre which develop the technique and with the biggest experience.

We also confirm in this study the benefits of BPA on functional capacity with a dramatic improvement of WHO functional class and 6MWD with an average gain of 93,5m, which is much higher than the *Minimally Important Difference*, estimated at 38,6m in pulmonary arterial hypertension patients (31). This improvement is superior to that observed for inoperable patients treated with riociguat (39m) (10) and compared with that reported for patients undergoing PEA (32) (97 m). Nt-proBNP plasma level were drastically improved by BPA, translating a reduction of right ventricle failure after BPA as reported previously by *Kriechbaum SD et al.*, who described a correlation between the decrease in NT-proBNP level and reduction in PVR and mPAP (30).

We also report an improvement of HRQOL evaluated by the SF-36v2 and MLHFQ scores which were both improved by BPA, confirming data from a previous study (33). Nevertheless both studies were of relatively limited sample size and their findings warrant confirmation on a larger scale.

Finally, our results suggest the benefits of the technique for all patient with inoperable CTEPH. No patient was refuted for BPA in our study regarding age; 22 patients included were then over 75 years old.

Complications and safety of BPA

With a complication rate of 11,6% of the 197 sessions and no peri-procedural death or severe complication requiring mechanical ventilation, embolization, or extra-corporeal life support, our study confirm the recent data suggesting that the development of the technique has allowed a deep reduction of complications, far above the first study of Fensterstein et al. (13).

Nevertheless, about one third of patient experienced a complication during the whole treatment, among which minor haemoptysis came first with 52% of them. Haemoptysis required only surveillance and oxygen therapy in all cases. This results are in accordance with a recent large cohort results ⁽¹⁴⁾. The reperfusion pulmonary edema rate is low in our study, and lower than previous studies as demonstrated in our meta-analysis (*supplementary files, figure 10*). This difference might be explained by the definition chosen for the assessment of this complication. We decided to define reperfusion pulmonary edema as a pulmonary edema following a BPA procedure that required specific therapy (diuretics, oxygen therapy, non-invasive continuous ventilation) and a prolongation of the hospitalization stay. This definition is different from previous studies, which define reperfusion pulmonary edema as X-ray opacity in the lung segment treated with BPA, independently of the clinical status of the patient.

We report original data on x-ray exposure induced by BPA. If no clinical impact of radiation has been noticed during the treatment and the follow-up, the radiation exposure induce by BPA is high, and is equivalent or higher than a coronary angiogram associate to an ad hoc percutaneous coronary intervention ⁽³⁴⁾ (*Table 7, Supplementary files*). Moreover, this radiation is repeated four time in mean for the whole treatment. This high radiation exposure might train cutaneous complications. Indeed, Balter et al reported multiples skin injury induced by fluoroscopically guided interventional procedures, which can lead to multiple surgery, and long and hardly treatable pain ^(35,36). This consideration should compel us to minimizing the likelihood and severity of radiation effects. Miller DL et al. suggested good practice procedure to avoid them including search of risk factors, monitoring of the radiation dose, advice of the patient and limitation as possible of the irradiation dose ⁽³⁷⁾. In our study, the notification threshold (30000cGy.cm²) and the patient follow-up threshold (50000 cGy.cm²) recommended in guideline ⁽³⁸⁾ for dose area product have been exceed in 7 (3,6%) and 1 sessions (0,5%) respectively. Concerning air kerma, the notification threshold (3000mGy) and the patient

follow-up threshold (5000 mGy) have been exceeded in 3 (1,6%) and 2 sessions (1,1%) respectively.

If determinist effects and skin injury are well understood, stochastic effects and impact of cumulative ionizing radiation are poorly described. However, a recent study in a population of adults with congenital heart disease reported that cumulative low-dose ionizing radiation was independently associated with cancer, with a possible dose related response ⁽³⁹⁾. Then patients with a cumulative ED>55mSv have a 2,67 fold risk of cancer than patient with a cumulative ED of less than 15mSv. These data should be taken with attention, as the median cumulative effective dose in our study was 68mSv per patient, and do not include all imaging used for the diagnosis and follow-up of the patient. However, these data should not question the usefulness of angioplasty as the midterm risk/benefits ratio is clearly in favour of BPA, but should push to limit radiation at a maximum, whether for the diagnosis or treatment of these patients.

Limitations of the study

Our study comports several limitations. Firstly, the design of the study is a prospective registry of all BPA patients, and 70% were treated by specific PH therapy. Neither primary nor meta-analysis of retrospective or prospective cohort studies can provide direct evidence on the benefits of BPA for CTEPH. Randomized controlled trials are ongoing to provide robust evidence on effectiveness and safety of BPA: RACE (ClinicalTrials.gov identifier NCT02634203) and MR BPA trials (UMIN Clinical Trials Registry identifier: UMIN000019549). Then, the follow-up of patient does not exceed 1 year, and we then don't know the long-term benefits of this procedure. Furthermore, the interpretation of the meta-analysis is inevitably limited by substantial between-study heterogeneity, in terms of selection criteria, BPA indication, disease severity, prevalence of comorbid conditions, timing of enrolment, and operator experience. In addition, outcome assessment could not be blinded to the pre-/post-BPA period, with the potential for evaluation bias. We cannot exclude that

procedure-related complications were under-reported or under-detected as patient follow-up was left to the discretion of operators. Finally, we get some missing data, especially for the HRQOL surveys, and even if the patients have not been selected, HRQOL result could't not reflect the impact of BPA on the whole cohort.

CONCLUSIONS

Despite a much older study population, BPA yielded functional and hemodynamic improvements in CTEPH patient ineligible for PEA, that were consistent with previous European studies. Even if the peri-procedural complication rate is not negligible, our study confirms the safety of BPA with the absence of complication requiring invasive management. Particular attention should nevertheless be paid to the x-ray exposure induced by BPA.

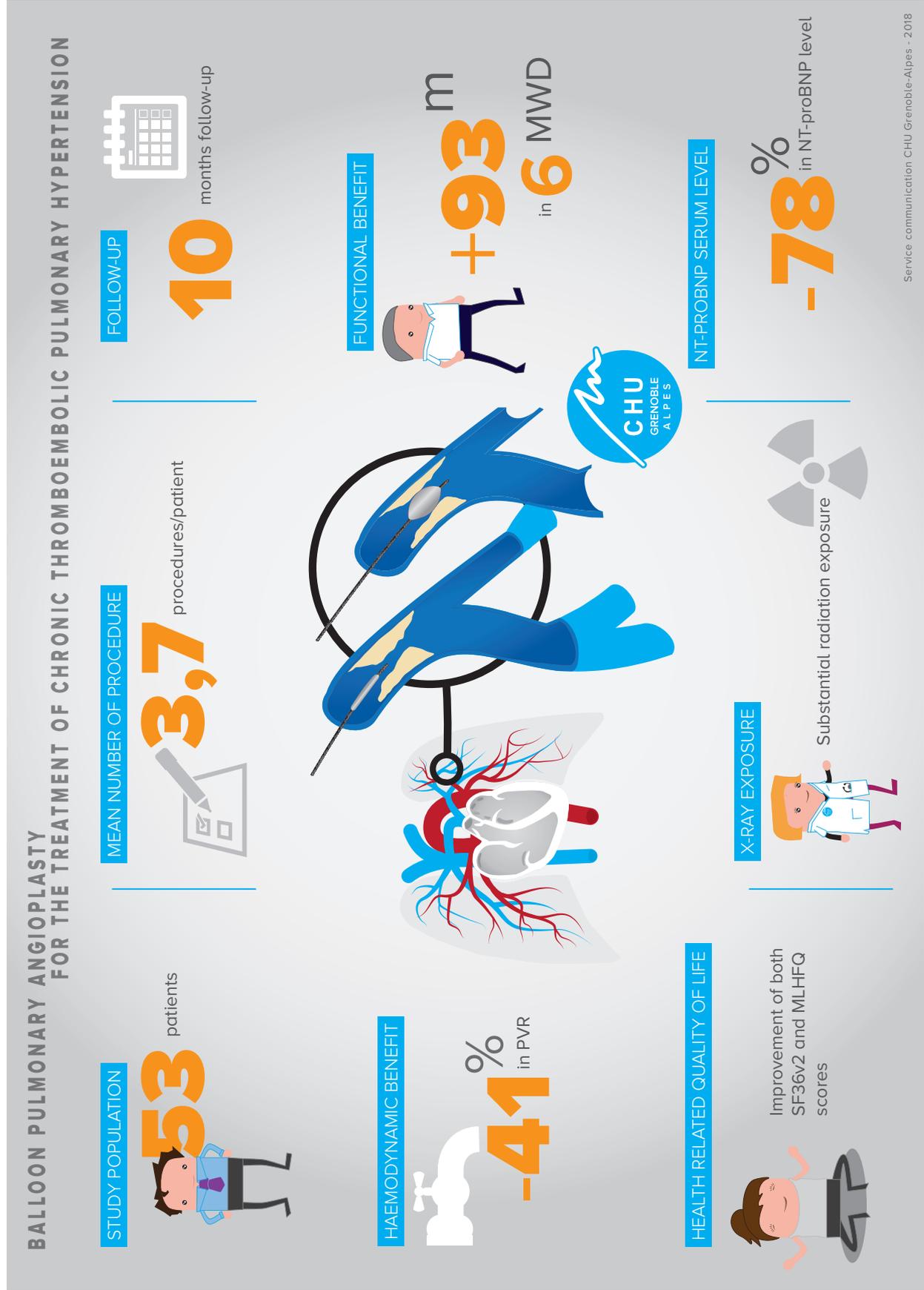
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Take-home figure



Supplementary files

Table 5: paired comparisons of medical therapy use at baseline and follow-up..

| Medical therapy* | No. patients | Baseline | Follow-up | <i>P</i> | Bonferroni-adjusted <i>P</i> |
|--------------------------------------|--------------|----------|-----------|----------|------------------------------|
| Endothelin-receptor antagonist | 48 | 22 (46) | 19 (40) | .41 | .99 |
| Soluble guanylate cyclase stimulator | 49 | 17 (35) | 16 (33) | .76 | .99 |
| Phosphodiesterase type-5 inhibitor | 48 | 15 (31) | 11 (23) | .29 | .99 |
| Prostacyclin analogue | 49 | 1 (2.0) | 0 (-) | .99 | .99 |
| ≥ 1 PAH-targeted drugs | 49 | 37 (76) | 34 (69) | .45 | .99 |
| Diuretics | 50 | 31 (62) | 20 (40) | .01 | .07 |
| Oxygen | 50 | 19 (38) | 16 (32) | .38 | .99 |

Abbreviations: PAH = pulmonary arterial hypertension.

* Values are numbers (%). Follow-up values were missing for therapy with endothelin-receptor antagonist (n=5), soluble guanylate cyclase stimulator (n=4), phosphodiesterase type-5 inhibitor (n=5), prostacyclin analogue (n=4), ≥ 1 PAH-targeted drugs (n=4), diuretics (n=3), and oxygen (

Table 6: Overview of primary studies of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension.

| Author, year | Feinstein, 2001 | Inami, 2014 | Kinutani 2014 | Aoki, 2017 | Ogo, 2017 | Kimura, 2017 |
|-------------------------------------|-----------------|-------------|---------------|------------|------------|--------------|
| Country | USA | Japan | Japan | Japan | Japan | Japan |
| Study sites, <i>n</i> | 1 | 2 | 1 | 1 | 1 | 1 |
| Enrolment period | 1994–1999 | 2009–2013 | 2012–2015 | 2009–2016 | 2011–2015 | 2012–2016 |
| Participants, <i>n</i> | 18 | 103† | 28 | 77 | 80 | 67‡ |
| Age, <i>year</i> | 52 (12) | 63 (14) | 65 (12) | 65 (14) | 67 (14) | 62 (14) |
| Female gender, <i>n</i> (%) | ... (...) | 79 (77) | 19 (68) | 63 (82) | 59 (74) | 46 (69) |
| History of PEA, <i>n</i> (%) | ... (...) | 11 (11) | 0 (-) | ... (...) | 6 (8) | ... (...) |
| WHO functional class, <i>n</i> (%) | | | | | | |
| I-II | 0 (-) | 13 (13) | 8 (29) | 52 (68) | 3 (4) | 10 (15) |
| III | 14 (78) | 74 (72) | 16 (57) | 18 (23) | 70 (87) | 51 (76) |
| IV | 4 (22) | 16 (15) | 4 (14) | 7 (9) | 7 (9) | 6 (9) |
| No. BPA sessions | 2.7 (1.2) | 3.4 (1.5) | 3.0 (1.4) | 5.0 (2.5) | 4.8 (2.1) | 6.0 (2.0) |
| Mean PAP, <i>mmHg</i> | 42 (12) | 41 (11) | 34 (10) | 38 (10) | 42 (11) | 39 (11) |
| PVR, <i>Wood units</i> | ... (...) | 8.9 (4.9) | 7.2 (4.0) | 7.3 (3.2) | 11.0 (5.3) | 9.7 (6.8) |
| Cardiac index <i>L/min/m</i> | 2.0 (0.4) | 2.5 (0.5) | ... (...) | 2.7 (0.7) | 2.3 (0.6) | ... (...) |
| 6MWD, <i>m</i> | 191 (...) | 342 (122) | 303 (92) | 380 (138) | 327 (124) | 322 (109) |
| BNP, <i>pg/mL</i> | ... (...) | 123 (143) | 160 (233) | 100 (147) | 227 (282) | 251 (487) |
| NT-proBNP, <i>pg/mL</i> | ... (...) | ... (...) | ... (...) | ... (...) | ... (...) | ... (...) |
| Length of follow-up, <i>month</i> * | ... (...) | 14 (11) | ... (...) | 6 (...) | 3 (...) | 6.8 (1) |

Table 6 (continued)

| Author, year | Yamasaki, 2017 | Yamagata, 2017 | Kwon, 2018 | Broch, 2016 | Kurzyna, 2017 | Kriechbaum, 2017 |
|-------------------------------------|----------------|----------------|-------------|-------------|---------------|------------------|
| Country | Japan | Japan | Korea | Norway | Poland | Germany |
| Study sites, <i>n</i> | 1 | 1 | 1 | 1 | 1 | 1 |
| Enrolment period | 2012–2015 | 2013–2016 | 2015–2017 | 2003–2014 | ... | 2014–2016 |
| Participants, <i>n</i> | 20 | 19 | 15 | 26# | 56† | 51 |
| Age, <i>year</i> | 62 (11) | 68 (9) | 53 (18) | 59 (12) | 59 (18) | 63 (11) |
| Female gender, <i>n</i> (%) | 16 (80) | 16 (84) | 7 (47) | 15 (58) | 28 (50) | 28 (55) |
| History of PEA, <i>n</i> (%) | ... (...) | ... (...) | 6 (40) | ... (...) | 9 (16) | 4 (8) |
| WHO functional class, <i>n</i> (%) | | | | | | |
| I-II | 2 (10) | 3 (16) | 6 (40) | 6 (23) | 3 (5) | 2 (4) |
| III | 17 (85) | 16 (84) | 5 (33) | 16 (62) | 41 (73) | 31 (61) |
| IV | 1 (5) | 0 (-) | 4 (27) | 4 (15) | 12 (22) | 18 (35) |
| No. BPA sessions | 2.7 (1.6) | 3.2 (1.6) | 3.5 (...) | 4 (2) | 3.8 (...) | 5 (...) |
| Mean PAP, <i>mmHg</i> | 43 (11) | 40 (9) | 41 (13) | 44 (11) | 51 (12) | 39 (12) |
| PVR, <i>Wood units</i> | 8.0 (2.8) | 7.5 (2.8) | 7.6 (5.6) | 7.6 (3.5) | 10.1 (3.9) | 6.4 (2.7) |
| Cardiac index, <i>L/min/m</i> | 3.1 (0.9) | ... (...) | 2.9 (0.8) | ... (...) | 2.4 (0.6) | 2.5 (0.6) |
| 6MWD, <i>m</i> | 391 (75) | 308 (88) | 387 (86) | 298 (105) | 304 (164) | 367 (125) |
| BNP, <i>pg/mL</i> | 66 (61) | ... (...) | ... (...) | ... (...) | ... (...) | ... (...) |
| NT-proBNP, <i>pg/mL</i> | ... (...) | 347 (441) | 2085 (2571) | 911 (1188) | 3746 (7160) | 948 (1311) |
| Length of follow-up, <i>month</i> * | 2.9 (1.6) | ... (...) | ... (...) | 3 (...) | (range, 3–6) | 6 (...) |

Table 6 (continued)

| Author, year | Present study |
|------------------------------------|---------------|
| Country | France |
| Study sites, <i>n</i> | 1 |
| Enrolment period | 2014–2016 |
| Participants, <i>n</i> | 53 |
| Age, year | 71 (12) |
| Female gender, <i>n</i> (%) | 28 (53) |
| History of PEA, <i>n</i> (%) | 5 (9) |
| WHO functional class, <i>n</i> (%) | |
| I-II | 9 (17) |
| III | 33 (62) |
| IV | 11 (21) |
| No. BPA sessions | 3.7 (1.4) |
| Mean PAP, mmHg | 45 (11) |
| PVR, Wood units | 8.9 (4.6) |
| Cardiac index, L/min/m | 2.3 (0.5) |
| 6MWD, m | 316 (155) |
| BNP, pg/mL | ... (...) |
| NT-proBNP, pg/mL | 2138 (3940) |
| Length of follow-up, month* | 10 (5) |

Values are mean (standard deviation) unless stated otherwise.

Abbreviations: 6MWD = 6-minute walking distance; BNP = B-type natriuretic peptide; BPA = balloon pulmonary angioplasty; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAP = pulmonary arterial pressure; PEA = pulmonary endarterectomy; PVR = pulmonary vascular resistance; WHO = World Health Organization.

* Length of follow-up was time from first (Inami, 2014) or last (Aoki 2017; Ogo, 2017; Kimura, 2017; Yamasaki, 2017; Broch, 2016; Kurzyna, 2017; present study) BPA session to follow-up right heart catheterization.

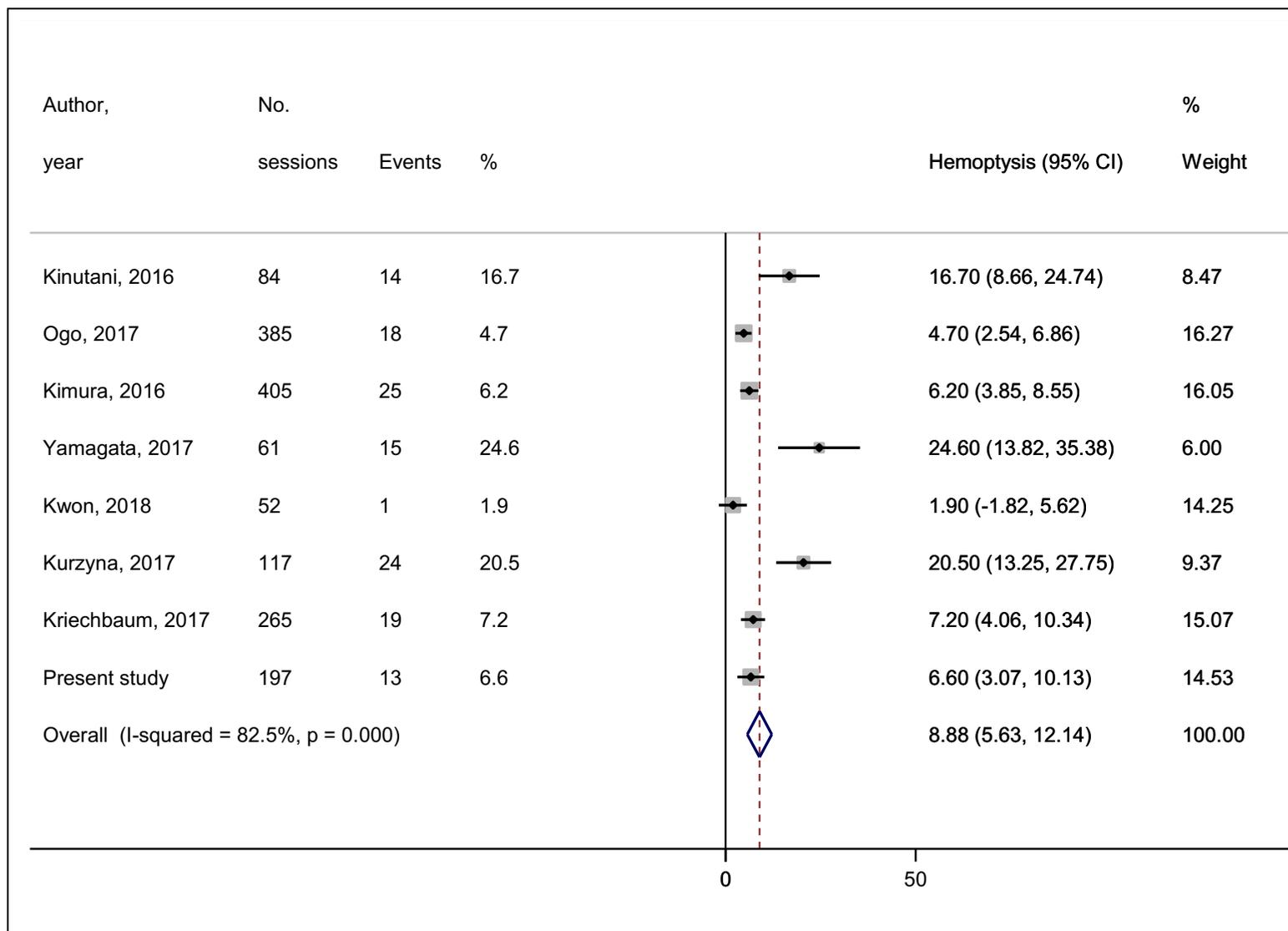
† Of 103 patients who underwent BPA, 83 completed follow-up.

‡ Of 101 patients who underwent BPA, 37 were excluded from the analysis (i.e., two patients who died before the final assessment due to non-BPA related disease, 16 patients with missing baseline hs-TnT levels, four patients with left heart disease [history of myocardial infarction, stable angina, mitral regurgitation, or hypertrophic cardiomyopathy], 11 patients who had not yet undergone 6-month follow-up, and one patient who did not undergo 6-month follow-up). Finally, the analytical sample included 67 patients who were followed up for 6 months after last BPA session.

Of 32 patients who were assigned to treatment with BPA, six were excluded from the analysis (i.e., two patients who died shortly after the first BPA procedure and four additional patients without echocardiography data). Finally, the analytical sample included 26 patients who were alive and transplant-free after BPA procedures.

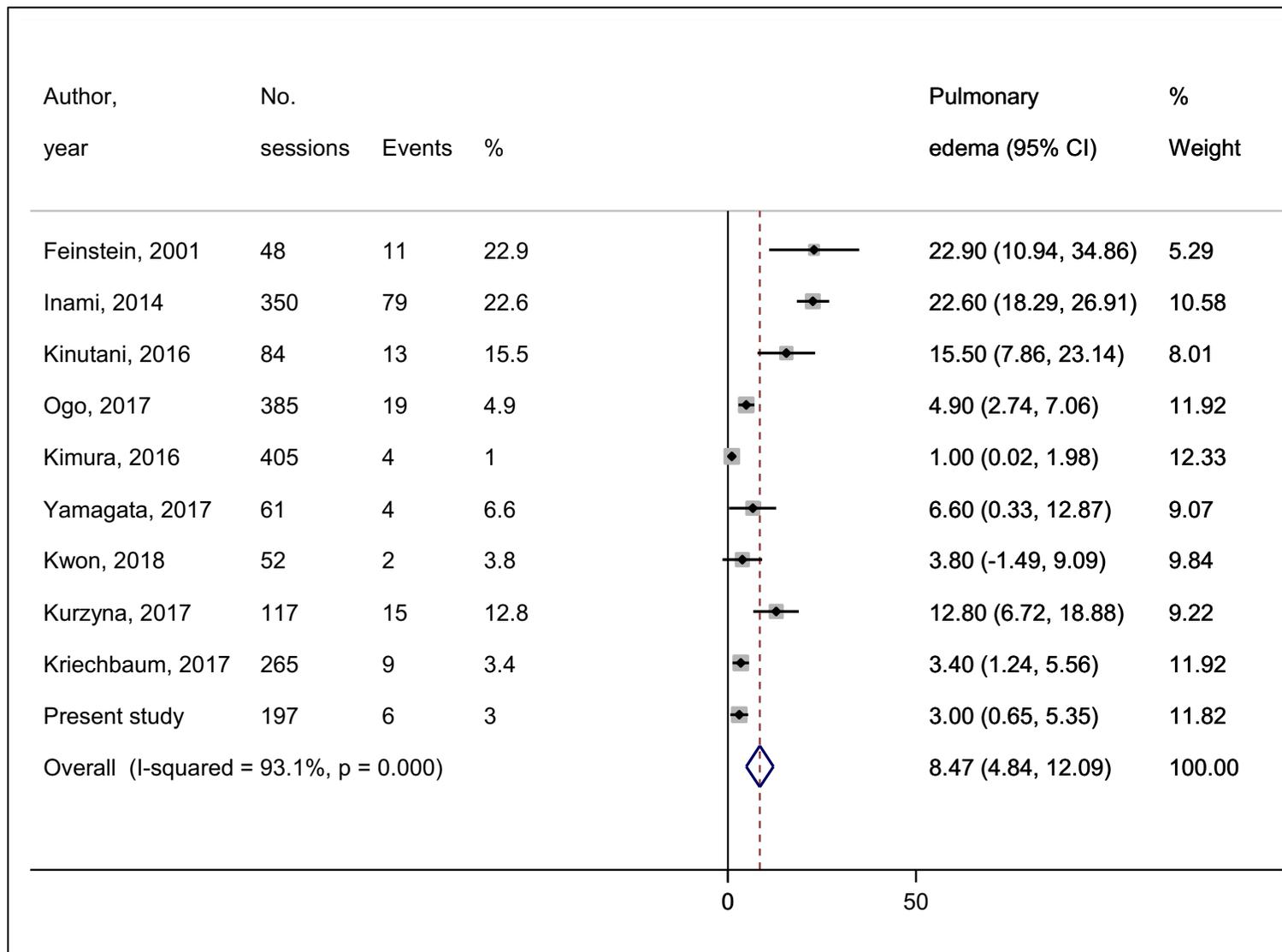
¶ Of 56 patients who underwent BPA, 31 completed follow-up.

Figure 9: Random-effect summary estimate of hemoptysis incidence.



Abbreviations: CI = confidence interval.

Figure 10: Random-effect summary estimate of pulmonary edema incidence.



Abbreviations: CI = confidence interval.

Table 7: Comparison of radiation dose indicators for different cardiac procedures

| | | BPA (present study) | CA alone * | CA + Ad hoc PCI **† | Elective PCI **‡ |
|--|--------------|---------------------|------------------|---------------------|-------------------|
| Dose area product (Gy.cm ²) | Median (IQR) | 101,2 (65,2-137,8) | 27,2 (15,5-45,2) | 58,0 (34,1-95,8) | 47,8 (26,34-85,9) |
| | Range | 4,7-658,3 | 0,1-610,8 | 1,0-1293,0 | 2,3-1000,9 |
| Cumulative air kerma (mGy) | Median (IQR) | 900 (556-1331) | 421 (240-695) | 1083 (619-1808) | 877 (472-1635) |
| | Range | 73-11408 | 17-9146 | 40-17011 | 17-11873 |
| Fluoroscopy time (min) | Median (IQR) | 41 (31-53) | 3,7 (2,3-6,3) | 10,3 (6,7-16,0) | 10,4 (6,2-17,8) |
| | Range | 2-92 | 0,1-77,0 | 1,0-124,9 | 0,7-122 |

Abbreviations: IQR=Interquartile range; BPA=Balloon Pulmonary Angioplasty; CA=Coronary Angiogram; PCI=Percutaneous Coronary Intervention

* Data for CA, CA + Ad hoc PCI, and elective PCI are extract from the RAY'ACT study ⁽³⁴⁾

†Ad hoc PCI referred to a PCI performed immediately after a CA in the same session

‡Elective PCI referred to a PCI in a separate session

BALLOON PULMONARY ANGIOPLASTY FOR THE TREATMENT OF CHRONIC
THROMBOEMBOLIC PULMONARY HYPERTENSION:
RESULTS OF THE GRENOBLE EXPERIENCE

ABSTRACT:

Aims: Balloon pulmonary angioplasty (BPA) is an emerging technique for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) for patient not eligible for a pulmonary endarterectomy that needs further evaluation.

Methods: All consecutive patients who underwent BPA in a French centre between January 2014 and September 2016 were evaluated prospectively before BPA and between 6 and 12 months after the last treatment session on functional, biological parameters, hemodynamic and health-related quality of life (HRQOL).

Results: 53 patients underwent a mean number of 3.7 sessions during 72.5 ± 68.8 days. The follow-up was performed at 303 ± 152 days. BPA improved WHO functional class, 6-min walk distance (mean difference, 94 m, 95% CI, 56 to 131), and NT-proBNP plasma level (1872.7 ± 3898.9 vs 405.7 ± 675.8 pg/mL, $p=0.01$). Hemodynamic parameters, including mPAP (-11 mmHg, 95% CI, -14 to -7.7), PVR (-3.8 WU, 95% CI, -5.1 to -2.6), and cardiac index ($0.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, 95% CI, 0.1 to 0.5) improved at follow-up. HRQOL evaluated by the SF36v2 and MLHFQ questionnaires was also enhanced by BPA. Complication rate was low with 6.6% of haemoptysis and 3% of reperfusion pulmonary oedema in a session-based analysis. X-ray exposure was significant with a median cumulative Air Kerma of 900mGy (IQR=556-1331mGy) and a median dose area product of 10115cGy.cm² (IQR=6523-13779cGy.cm²) per session.

Conclusion: BPA improves functional and exercise capacity, hemodynamic parameters and quality of life in CTEPH patients not eligible for pulmonary endarterectomy. Complication rate was low and included only minor complications.

KEYWORDS: Balloon pulmonary angioplasty, Chronic thromboembolic pulmonary hypertension, quality of life, x-ray exposure, right heart catheterisation, SF36.

SECTION: Cardiology

L'ANGIOPLASTIE PULMONAIRE PERCUTANÉE POUR LE TRAITEMENT DE
L'HYPERTENSION PULMONAIRE THROMBOEMBOLIQUE CHRONIQUE :
RÉSULTATS DE L'EXPÉRIENCE INITIALE GRENOBLOISE.

RÉSUMÉ :

Objectifs : L'angioplastie pulmonaire percutanée (ATL-P) est une technique innovante pour le traitement de l'hypertension pulmonaire thromboembolique chronique (HTP-TEC) chez les patients inéligibles à une thromboendartériectomie chirurgicale. Cette technique nécessite cependant des évaluations complémentaires.

Méthodes : Tous les patients traités par ATL-P entre janvier 2014 et septembre 2016 ont été évalués par des paramètres fonctionnels, biologiques, hémodynamiques et de qualité de vie avant le traitement et entre 6 et 12 mois après la dernière procédure.

Résultats : 53 patients consécutifs ont bénéficié d'un nombre moyen de 3,7 sessions au cours d'une période de $72,5 \pm 68,8$ jours. L'ATL-P améliore la classe fonctionnelle NYHA, le test de marche de 6 minutes (différence absolue, 94 m, IC95%, 56 to 131), et le taux sérique de NT-proBNP ($1872,7 \pm 3898,9$ vs $405,7 \pm 675,8$ pg/mL, $p=0,01$). Les paramètres hémodynamiques incluant la pression artérielle pulmonaire moyenne (-11 mmHg, IC95%, -14 to -7.7), les résistances vasculaires pulmonaires (-3.8 WU, IC95%, -5.1 to -2.6), et l'index cardiaque ($0.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, IC95%, 0.1 to 0.5) sont améliorés par l'ATL-P. La qualité de vie évaluée par les scores SF-36v2 et MLHFQ est elle aussi améliorée lors du suivi. Le taux de complication par session était faible avec un taux d'hémoptysie de 6,6% et un taux d'œdème de reperfusion de 3%. L'irradiation induite par les procédures était significative.

Conclusion : L'ATL-P améliore les paramètres fonctionnels, hémodynamiques et de qualité de vie chez les patients atteints de HTP-TEC et inéligibles à un traitement chirurgical, avec un taux de complications faible.

MOTS-CLES : Angioplastie pulmonaire percutanée, Hypertension pulmonaire thromboembolique chronique, Qualité de vie, Irradiation, Cathétérisme cardiaque droit, SF-36.

FILIÈRE : Cardiologie et Maladies Vasculaires

THESE SOUTENUE PAR : Nicolas PILIERO

TITRE : L'angioplastie pulmonaire percutanée pour le traitement de l'hypertension pulmonaire thromboembolique chronique : Résultats de l'expérience initiale Grenobloise.

CONCLUSION

L'angioplastie pulmonaire percutanée est une technique innovante pour le traitement de l'hypertension pulmonaire thromboembolique chronique (HTP-TEC) chez les patients non éligibles à une thromboendartérectomie chirurgicale développée au CHU de Grenoble depuis 2014 (projet OCTEPH, CHU promoteur, clinicaltrial n°NCT02844036). Dans cette série prospective monocentrique de 53 patients consécutifs inclus entre Janvier 2014 et Septembre 2016, les patients ont bénéficié de 3,7 procédures (2 à 7 procédures), au cours d'une période de $72,5 \pm 68,8$ jours. La moyenne d'âge des patients était de $70,9 \pm 12,3$ ans (37 à 88ans). 70% des patients bénéficiaient en amont d'un traitement médical spécifique de l'HTAP. Les patients ont été évalués sur le plan clinique, fonctionnel, biologique et hémodynamique avant le début du traitement puis à 303 ± 152 jours après la dernière procédure.

Dans notre étude, les bénéfices de l'angioplastie pulmonaire percutanée sont nombreux. Sur le plan fonctionnel, on observe une amélioration de la classe NYHA avec seulement 12,5% des patients en classe NYHA 3 ou 4 lors du suivi, contre 83,3% avant le début du traitement. Les capacités physiques sont également améliorées par ce traitement avec un gain moyen de 93,5m au test de marche de 6 minutes. Sur le plan biologique, on note une réduction drastique du taux de NT-proBNP sérique passant de $1872,7 \pm 3898,9$ pg/mL à $405,7 \pm 675,8$ pg/mL. Le bénéfice de cette technique est également significatif sur le plan hémodynamique avec une réduction de la pression artérielle pulmonaire moyenne de $44,8 \pm 11,9$ mmHg à $33,7 \pm 8,1$ mmHg et une amélioration de l'index cardiaque de $2,3 \pm 0,5$ L/min/m² à $2,6 \pm 0,6$ L/min/m². Il en résulte une réduction des résistances vasculaires pulmonaires de 44,2%. On note également une amélioration de la qualité de vie mesurée chez 29 des 53 patients, par les scores Short-Form 36v2 et MLHFQ (Minnesota Living with Heart Failure Questionnaire).

La tolérance de ce traitement est satisfaisante. Aucun patient n'est décédé au cours du suivi. Les complications sont principalement les hémoptysies, survenues dans 6,6% des procédures, et l'œdème pulmonaire de reperfusion, induit dans 3% des procédures. La sévérité de l'hypoxie a nécessité un traitement par ventilation non-invasive chez 3 patients. Aucun cas d'insuffisance rénale n'est à déplorer. L'exposition aux rayons-X chez les patients est conséquente, proportionnelle au nombre de séances et sans complication à court terme. Cependant l'importance des doses reçues nécessite un suivi à moyen et long terme afin de connaître d'éventuels effets stochastiques. La radioprotection des patients et des opérateurs est un enjeu important de cette technique.

L'angioplastie pulmonaire percutanée est donc un traitement efficace et sûr à moyen terme pour le traitement de l'HTP-TEC chez les patients non éligibles à une chirurgie conventionnelle. Nos résultats sont comparables aux études publiées jusqu'à aujourd'hui. Des études complémentaires et un suivi à long terme sont nécessaires pour préciser l'impact pronostic et la place de l'angioplastie pulmonaire percutanée dans la stratégie thérapeutique de l'HTP-TEC.

VU ET PERMIS D'IMPRIMER

Grenoble, le 14/05/2018

LE DOYEN
Le Doyen de l'UFR de Médecine

Pr. Patrice MORAND

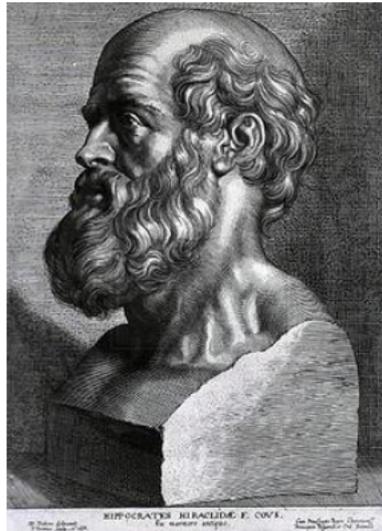
Patrice MORAND

LE PRESIDENT DE LA THESE


CENTRE HOSPITALIER REGIONAL
et UNIVERSITAIRE de GRENOBLE
Dr Gérald VANZETTO
CARDIOLOGIE

PROFESSEUR Gérald VANZETTO

SERMENT D'HIPPOCRATE



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.