Balloon Pulmonary Angioplasty in Patients With Chronic Thromboembolic Pulmonary Hypertension
— A Systematic Review and Meta-Analysis —

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Background: Balloon pulmonary angioplasty (BPA) is a percutaneous treatment option for patients affected by chronic thromboembolic pulmonary hypertension (CTEPH) and either judged inoperable or with persistent symptoms after pulmonary endarterectomy. Current data regarding BPA are sparse and results vary according to local center experience. A systematic review of the literature was performed to better understand the effectiveness and safety of BPA in the treatment of CTEPH.

Methods and Results: PubMed and EMBASE were searched for studies reporting BPA results in patients with CTEPH. Differences in clinical and hemodynamic parameters before and after the procedure were analyzed. Weighted mean proportion and 95% confidence intervals (CIs) of adverse events were calculated. In total, 14 studies were included (725 patients). BPA was associated with a reduction in mean pulmonary artery pressure (from 43 to 32.5 mmHg), reduction in pulmonary vascular resistance (from 9.94 to 5.06 Woods units), increase in cardiac index (from 2.35 to 2.62 L/min/m²), and improvement of 6-minute walking distance (from 345 to 442 m). Periprocedural mortality occurred in 2.1% of patients (95% CI 0.8–4.1) while reperfusion and pulmonary vessel injuries occurred in 9.3% (95% CI 3.1–18.4) and 2.3% (95% CI 0.9–4.5) of total BPA sessions, respectively.

Conclusions: Our systematic review suggested that BPA for CTEPH patients was an effective and relatively safe treatment option.

Key Words: Balloon pulmonary angioplasty; Chronic thromboembolic pulmonary hypertension; Pulmonary embolism; Pulmonary endarterectomy

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as the persistence of thrombi and vascular remodeling in the pulmonary circulation associated with a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg.1,2 It affects 0.5–4% of patients within 2 years of the first episode of pulmonary embolism (PE).3 CTEPH has a poor prognosis because it produces high pulmonary vascular resistance (PVR) leading to right heart failure and death.4 Patients with untreated CTEPH are likely to develop progressive disease and, therefore, all patients should receive appropriate treatment.5

Pulmonary endarterectomy (PEA) is the treatment of choice in symptomatic patients, but operability assessment excludes approximately 30% of eligible patients, because of peripheral lesions, extreme PVR or high surgical risk. Moreover, one-third of surgical patients still suffer from residual pulmonary hypertension and symptoms after surgery (recurrent or persistent CTEPH).6,7 In these cases, options for alternative treatment consist of life-long anticoagulant therapy, oxygen supply and a pulmonary vasodilator such as the soluble guanylate cyclase agonist, riociguat.8,9

Balloon pulmonary angioplasty (BPA) is a percutaneous technique aimed at widening stenotic or opening obstructed pulmonary arteries with a balloon catheter guided by fluoroscopy. It has already been established in patients with congenital pulmonary stenosis, but is now emerging as an alternative treatment of symptomatic CTEPH patients.10 However, current data regarding the efficacy and feasibility of BPA are sparse and results vary according to local center experience.

We performed a systematic review and meta-analysis to better understand the effectiveness and safety of BPA in the treatment of CTEPH.

Methods
The systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.11

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Search Strategy
Two investigators (M.R.B. and G.Z.) independently searched PubMed and EMBASE, without language restriction, from database inception until 30 November 2017, for studies reporting BPA results in CTEPH patients. We used the following search terms as textword or MeSh: “Pulmonary artery”, “Pulmonary embolism”, “Pulmonary hypertension”, “Chronic”, “Angioplasty”, “Balloon”. Reference lists of included articles and those relevant to the topic were hand-searched for identification of additional, potentially relevant articles.

Study Selection and Eligibility Criteria
We included all full-text studies reporting outcome of BPA performed in inoperable, persistent, or recurrent CTEPH. Specifically, we selected studies enrolling at least 5 patients reporting the following data: (1) total number of patients or total number of BPA sessions or the number of sessions per patient; (2) at least 1 hemodynamic measurement among mPAP, PVR and cardiac output or index (CO/CI) or exercise capacity evaluated as New York Heart Association functional class (NYHA) and/or 6-minute walking distance (6MWD); and (3) hemodynamic measurements and/or clinical characteristics reported both before the first BPA session and after the last procedure. To increase consistency, we focused on studies reporting results immediately or up to 6 months after the last BPA session.

To assess the safety of the procedure, studies reporting BPA complications were also included. If at least 2 papers from the same institution were present, the corresponding author was contacted to avoid duplicates, and publication with the most recent and/or the largest sample size was included. Two investigators (G.Z. and M.R.B.) evaluated the titles and abstract of all selected references. Articles that met the initial eligibility criteria were selected for full-text screening and review. Discrepancies were resolved by a third investigator (V.P.). Conference abstracts were excluded. Only 1 abstract satisfying all 3 conditions listed was included.12

Data Extraction
One author (M.R.B.) extracted data using a standardized spreadsheet under the supervision of a second investigator (G.Z.). Demographic characteristics (age and sex of patients, BPA indication, and concomitant pulmonary vasodilator medical therapy) are reported in Supplementary Table 1A. The following data were extracted (Supplementary Table 1B): (1) author, year, country and affiliation; (2) number of patients, number of BPA sessions or sessions per patient; (3) hemodynamic measurements before and after BPA (mPAP, PVR and CI); (4) exercise capacity before and after BPA (NYHA and 6MWD); (5) time at which hemodynamic measurements and clinical characteristics were reassessed after the last procedure; and (6) periprocedural complications, defined as pulmonary artery dissection or perforation, reperfusion injury (i.e., post-
Results

The search identified 1,084 potentially eligible studies. After excluding 941 papers through title and abstract selection, 97 from full-text examination and 7 duplicates, 40 studies were included (Figure 1, Supplementary Table 1B). The database search produced only retrospective observational studies. Among studies from the same affiliation, we selected the most recent and/or the largest sample size study according to the outcome measured. These studies included:

- 6 cohorts from Keio University School of Medicine, Tokyo, Japan
- 5 cohorts from Tohoku University Graduate School of Medicine, Sendai, Japan
- 3 cohorts from National Cerebral and Cardiovascular Center, Suita, Japan
- 2 cohorts from National Hospital Organization Okayama Medical Center, Japan
- 2 cohorts from Oslo University, Norway
- 6 multicenter studies from Keio and Kiorin University School of Medicine, Tokyo, Japan
- 1 multicenter study from Tohoku University, Tokyo University, Kyorin University, Mie University, National Cardiovascular Research Center, Kobe University, National Hospital Organization Okayama Medical Center (Japan)
- 1 multicenter study from Tokyo Women’s Medical University and Kyushu University, Fukuoka (Japan)

Study Characteristics (Supplementary Table 1A)

The largest group of treated patients was 308, while the smallest study comprised 7 patients. Median number of patients per study was 26. Median patient age was 63 years and 73% were female. Most of the studies (31 of 40) were performed in Japan, 8 in Europe (Norway, Poland, Russia, Germany and Spain) and 1 in the USA. When reported, the main indication to perform BPA was inoperable disease. A small proportion of the total number was treated with procedural pulmonary edema, visualized on chest X-ray or requiring supplemental oxygen and diuretics, mechanical ventilation, or cardiopulmonary support) and/or periprocedural mortality. Definitions of periprocedural complications are shown in Supplementary Table 2.

Efficacy and Safety Outcomes

The efficacy outcome was the change from baseline of hemodynamic measurements (mPAP, PVR and CI) and exercise capacity (6MWD and NYHA). The safety outcome was the rate of periprocedural complications.

Risk of Bias Assessment

The Newcastle Ottawa Scale (NOS) was used to assess the quality of included studies. The NOS assigns a maximum of 9 points based on 3 quality parameters: selection, comparability, and outcome, with a cutoff ≤5 being indicative of high risk of bias. The risk of bias ratings for each study is reported in Supplementary Table 3.

Statistical Analysis

For assessing efficacy outcomes, we calculated and compared the median of the mean values reported in each single study before and after BPA; 2 studies reporting values as median were excluded from the final analysis. Weighted mean proportion and 95% confidence intervals (CoI) of adverse events were calculated; these data were pooled using a random-effects model, given the high statistical heterogeneity. Statistical heterogeneity was evaluated using the I² statistic, which assesses the appropriateness of pooling the individual study results. The I² value provides an estimate of the amount of variance across the studies as a result of heterogeneity rather than chance. I² <30% indicates mild heterogeneity, 30–50% moderate and >50% severe heterogeneity. A funnel plot of the effect size vs. the standard error was designed, to highlight possible publication bias. The analysis was performed using StatsDirect (Version 2.7; StatsDirect Ltd, Altrincham, UK).

Figure 2. Hemodynamic parameters (A–C) and 6-minute walking distance (D) before and after BPA procedure. BPA, balloon pulmonary angioplasty; CI, cardiac index; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistances; 6MWD, 6-minute walking distance.
BPA because of recurrent or persistent PH after PEA or refusal to undergo PEA.

Risk of Bias
The quality of the observational studies was judged moderate (median=6; range: 3–6) (Supplementary Table 3), with the most common source of bias being the absence of a control group.

Analysis of Outcomes
Subsequent reporting of BPA patients from the same institution was analyzed and only the last report was considered. Thus, the final cohort included 14 studies with a total population of 725 patients (Supplementary Table 1C).12,23,28,39,42,44,51,52

Hemodynamic Parameters
Median of the mean mPAP was 43 mmHg (interquartile range (IQR) 40.5–49.25 mmHg) before BPA and 32.5 mmHg (IQR 25–33.5 mmHg) after BPA (Figure 2A). Median of the mean CI of included studies was 2.35 L/min/m² (IQR 2.23–2.70 L/min/m²) before BPA and 2.62 L/min/m² (IQR 2.5–2.92 L/min/m²) after BPA (Figure 2B). Median of the mean PVR decreased from 9.94 Woods units (IQR 7.58–13.5 Woods units) before BPA to 5.06 Woods units (IQR 4.7–21.7; I²=97.8%; Supplementary Figure 2) with a high risk of publication bias according to the funnel plot.

Exercise Capacity
Median of the mean 6MWD before BPA was 345 m (IQR 322–369 m), increasing to 442 m (IQR 403–466 m) after BPA (Figure 2D). Functional status (NYHA class) before and after BPA (Figure 3). Functional New York Heart Association (NYHA) class before and after balloon pulmonary angioplasty (BPA).

Complications
Complications were differently defined across the studies (Supplementary Table 2) and reported in 12 papers (Supplementary Table 3).12,15,18,28,34,42,44,46,49,51,52 According to the meta-analysis (Figure 4), periprocedural mortality was 2.1% (95% CI 0.8–4.1; I²=37.7%; random-effect model) with a low risk of publication bias according to the funnel plot. Meta-analysis was also performed for reperfusion and pulmonary vessel injuries. Reperfusion injuries occurred in 9.3% (95% CI 3.1–18.4; I²=97.8%; Supplementary Figure 1) and pulmonary vessel injuries in 2.3% of total BPA sessions (95% CI 0.9–4.5; I²=87.7%; Supplementary Figure 2). Funnel plots suggested a high risk of publication bias for the rate of reperfusion injuries and pulmonary vessel injuries. A combined analysis of reperfusion and vessel injuries was also performed. The composite endpoint occurred in 11.8% of total BPA sessions (95% CI 4.7–21.7; I²=97.8%; Supplementary Figure 3) with a high risk of publication bias according to the funnel plot.

Discussion
CTEPH is a form of PH related to the persistence of thrombi on pulmonary arteries after an embolic event with vascular remodeling of lung circulation.5–8 The reason for clot persistence even after adequate anticoagulation is still debated, possibly driven by impaired fibrinolysis, endothelial dysfunction, thrombophilia or supra-infection causing delayed resolution.54

CTEPH occurs in 0.5–4% of patients with a history of PE, commonly with a latent phase between PE and the onset of CTEPH symptoms.3 On the other hand, previous PE is confirmed in approximately 75% of CTEPH patients,6 while in the other 25% the first PE event probably passed unnoticed.

This is the only form of PH that is treatable with PEA, a surgical procedure that may cure the disease especially in patients with fresh or organized thrombi of the proximal branches of pulmonary arteries (types 1 and 2 of the surgical classification).55 However, many CTEPH patients are not suitable for surgery (high surgical risk or disease involving distal segmental arteries) or may display recurrent symptoms after PEA.6 For these patients, percutaneous BPA or medical therapy are the only options. There are no clear data on the use and benefit of BPA, with only case series or small registries published. The first BPA procedure was reported in 1988,56 but was abandoned early because of the high rate of complications. The procedure was then refined, and subsequent published data suggest a possible role in the management of CTEPH patients.

The present systematic review included patients who underwent BPA for inoperable CTEPH, for persistent/recurrent PH after surgery or for refusing of surgery. Other studies have reviewed the hemodynamic impact of BPA on CTEPH,57,58 but none have focused on complications. Overall, the included studies were only observational and the assessed quality by NOS scale was considered moderate.
Most of the data came from the same geographical area and the generalization of results is an open issue. We found that BPA increased the 6MWD and decreased functional (NYHA) class status, parameters possibly associated with an improvement in patients’ quality of life. A consistent reduction of mPAP and PVR, as well as an increase in CI, was also observed.

Alternatively, riociguat is the only drug showing a significant functional improvement in these patients; in the CHEST-1 trial (9) the reported mean increase in 6MWD was 46 m (range, 25–67). Mean decrease in mPAP was 5 mmHg (range, 3–7), mean decrease in PVR was 246 dyn/s/cm² (range, 190–303) and the mean increase in cardiac output was 0.9 mL/min (range, 0.6–1.1).

Comparison of results between BPA and medical treatment with riociguat must be done with caution and direct comparison is currently under investigation (www.clinicaltrial.gov: NCT02634203). In the meantime, the choice of BPA over riociguat may depend on several factors. In particular, BPA should be considered in high-volume CTEPH centers where expertise and adequate facilities are present. Moreover, in patients who are unresponsive...
or intolerant to vasodilator medical therapy, BPA might be the only treatment option. Conversely, procedural complications, technical challenges in complex cases and the need for several hospitalizations to perform each session (currently, 3–10 sessions are usually required for each patient) must be taken into account. However, PEA, BPA and medical treatment are not mutually exclusive, even if the mortality rate seems acceptable. Large, international, multicenter randomized controlled trials comparing optimal medical therapy with BPA in inoperable CTEPH patients are warranted to better determine the efficacy and safety of BPA.

Disclosures

No conflicts of interest are reported.

Conclusions

BPA has emerged as an adjunctive therapy for CTEPH patients who are inoperable or with persistent–recurrent symptoms after surgery. The present review highlighted the potential of BPA in improving both hemodynamic parameters and clinical performance, although the evidence is not high quality. Assessment of the complication rate was probably highly imprecise because of publication bias, even if the mortality rate seems acceptable. Large, international, multicenter randomized controlled trials comparing optimal medical therapy with BPA in inoperable CTEPH patients are warranted to better determine the efficacy and safety of BPA.

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**Supplementary Files**

Please find supplementary file(s):
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