



Meta-analysis of use of balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension



Muhammad Shahzeb Khan ^{a,*,1}, Emaan Amin ^{b,1}, Muhammad Mustafa Memon ^{b,1}, Naser Yamani ^{a,1}, Tariq Jamal Siddiqi ^{b,1}, Safi U. Khan ^{c,1}, Mohammad Hassan Murad ^{d,1}, Farouk Mookadam ^{e,1}, Vincent M. Figueredo ^{f,1}, Rami Doukky ^{g,1}, Raymond L. Benza ^{h,1}, Richard A. Krasuski ^{i,1}

^a Department of Internal Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL, USA

^b Department of Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan

^c Department of Internal Medicine, Robert Packer Hospital, Sayre, PA, USA

^d Evidence-based Practice Center, Mayo Clinic, Rochester, MN, USA

^e Department of Cardiovascular Diseases, Mayo Clinic, Scottsdale, AZ, USA

^f Sidney Kimmel College of Medicine at Thomas Jefferson University, Philadelphia, PA, USA

^g Division of Cardiology, Cook County Health and Hospitals System, Chicago, IL, USA

^h Cardiovascular Institute, Allegheny Health Network, Pittsburgh, PA, USA

ⁱ Department of Cardiovascular Medicine, Duke University Health System, Durham, NC, USA

ARTICLE INFO

Article history:

Received 11 November 2018

Received in revised form 5 February 2019

Accepted 22 February 2019

Available online 23 February 2019

Keywords:

Balloon pulmonary angioplasty
Chronic thromboembolic pulmonary hypertension
Meta-analysis

ABSTRACT

Background: Current guidelines give balloon pulmonary angioplasty (BPA) a Class IIb recommendation for use in inoperable chronic thromboembolic pulmonary hypertension (CTEPH), as its safety and efficacy remain poorly defined. We conducted a systematic review and meta-analysis to evaluate BPA effectiveness.

Methods: Medline, Cochrane Library and Scopus were searched for original studies from database inception dates until 24th May 2018. Prospective studies reporting outcomes before and after BPA in inoperable CTEPH patients were included. Studies with <20 patients were excluded. Data were pooled using a random effects model represented as weighted mean differences with 95% confidence intervals (CIs).

Results: Seventeen noncomparative studies comprising 670 CTEPH patients (mean age 62 years; 68% women) were included. Meta-analysis showed significantly decreased mean pulmonary artery pressure (-14.2 mm Hg [95% CI $-18.9, -9.5$]), pulmonary vascular resistance (-303.5 dyn·s/cm⁵ [95% CI $-377.6, -229.4$]) and mean right atrial pressure (-2.7 mm Hg [95% CI $-4.1, -1.3$]) after BPA. Six-minute walk distance (67.3 m [95% CI 53.8, 80.8]) and cardiac output (0.2 l/min [95% CI 0.0, 0.3]) were significantly increased following BPA. From 12 studies reporting mortality with median follow-up of 9 months after BPA (range, 1–51 months), pooled incidence of short (<1 month) and long-term mortality (>1 month) was 1.9% and 5.7%, respectively.

Conclusion: This systematic review and meta-analysis suggests mildly improved hemodynamics and overall low mortality rates following BPA in inoperable CTEPH patients. This non-comparative evidence can be used to facilitate decision making until the results of larger, controlled studies become available.

© 2019 Elsevier B.V. All rights reserved.

1. Introduction

Pulmonary thromboendarterectomy is the gold standard and potentially curative treatment for chronic thromboembolic pulmonary hypertension (CTEPH) patients [1]. However, over one third of patients are deemed inoperable [2]. The reasons for this include the presence of

significant comorbidities or the existence of mostly distal and therefore inaccessible obstruction. Balloon pulmonary angioplasty (BPA) has emerged as a potential therapeutic option for surgically inoperable CTEPH patients, receiving a class IIb recommendation (level of evidence C) in the current pulmonary hypertension guidelines [3]. The procedure aims to expand stenotic lesions or open obstructed vessels to restore pulmonary blood flow and improve hemodynamics, with the goal of decreasing right ventricular afterload and averting right ventricular failure, the most common cause of death in these patients [4].

During the last decade, several small, uncontrolled studies have been conducted to investigate outcomes and complications following BPA. However, due to the paucity of large, randomized controlled trials

* Corresponding author at: Department of Internal Medicine, John H. Stroger, Jr Hospital of Cook County, 1900 W Harrison St, Chicago, IL 60601, USA.

E-mail address: shahzebkhan@gmail.com (M.S. Khan).

¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

(RCTs), the safety and efficacy of BPA for inoperable CTEPH remain largely uncertain. To fill this knowledge gap, we therefore conducted a systematic review and meta-analysis of all available studies to evaluate BPA effectiveness.

2. Material and methods

2.1. Data sources and search strategy

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) guidelines [5]. Medline, Cochrane Library and Scopus were queried for original studies from database inception dates until May 2018, with no language or time restrictions. Key search terms employed included “chronic thromboembolic pulmonary hypertension” or “CTEPH” and “balloon pulmonary angioplasty” or “BPA”. The complete search strategy used in each database is outlined in the supplementary material (Supplementary Table 1). Proceedings of major scientific conferences and online library clinicaltrials.gov were also searched to identify grey literature. Reference lists of relevant review articles were also manually screened for additional studies. All citations were exported to Endnote Reference Manager (Clarivate Analytics, Philadelphia, PA; version X7.5) and duplicates were removed.

2.2. Study selection

The final list of articles was reviewed by two independent investigators (EA and MMM). Studies were initially selected based on title and abstract. Eligibility of inclusion was then confirmed by reviewing full-texts of selected studies. A third investigator (MSK) acted as a mediator to resolve any discrepancies. Prospective studies reporting at least one of our outcomes of interest before and after BPA in inoperable CTEPH patients were included. Studies with <20 participants were excluded.

2.3. Data extraction and assessment of study quality

Data were extracted by two independent reviewers (EA and MMM) using a standardized abstraction form. First author, year of publication, sample size, patient population, number of BPA sessions per patient, hemodynamic parameters, and mortality rates were collected. Outcomes of interest included procedure related complications, mean pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), mean right atrial pressure (RAP), six-minute walk distance (6-MWD), cardiac output (CO), stroke volume (SV), stroke volume index (SVI), heart rate (HR), New York Heart Association (NYHA) function class, oxygen saturation (SaO₂), glomerular filtration rate (GFR), creatinine (Cr) and mortality. Newcastle-Ottawa scale was used for risk of bias assessment of included studies [6].

2.4. Statistical analysis

RevMan (Cochrane Collaboration, Oxford, UK; Version 5.3) was used for all analyses. Continuous data were pooled to estimate weighted mean differences with 95% confidence intervals (CIs) using a random-effects model with inverse variance weighting [7]. In cases where only medians and interquartile ranges were reported, means and standard deviations (SDs) were approximated using the method described in the Cochrane Handbook [8]. Similarly, change in PVR reported as Woods units was converted to dyn·s/cm⁵ by multiplying by 80, and change in NT-proBNP reported in pmol/l was converted to pg/ml by dividing by 3.671. Heterogeneity across studies was evaluated using the I² statistic [9]; I² = 25–50%, 50–75%, and > 75% represented mild, moderate and severe heterogeneity, respectively. Visual inspection of the funnel plot and Egger's regression test were used to test for publication bias according to PAP. Open Meta-Analyst (Brown University School of Public Health, Providence, RI) was used to conduct random-effects meta-regression analysis to assess the contribution of female gender (%) to heterogeneity in outcomes with 10 or more studies (PAP, PVR, RAP, and 6-MWD). $p < 0.05$ was considered significant in all cases.

3. Results

3.1. Study characteristics and quality assessment

Seventeen prospective noncomparative observational studies comprising 670 CTEPH patients were included in the analysis. Fig. 1 shows the detailed literature search strategy. All studies had small ($n < 100$) sample sizes. Mean age of patients ranged from 57.0 to 70.0 years, with a median of 62.5 years. A median of 4 BPA sessions were carried out per patient across studies. On average, studies consisted of a majority (68.4%) of women. None of the studies reported proportions of races/ethnicities comprising the enrolled patients. Study characteristics and patient demographics are outlined in Table 1. Funnel plot and Egger's regression did not show evidence of publication bias for PAP

(p [2-tailed] = 0.787) (Supplementary Fig. 1). Methodological quality assessment of studies suggested high risk of bias, primarily due to the lack of a comparison group. (Table 2).

Five studies consisting of 167 patients reported procedure-related complications. The most common pooled periprocedural complication was reperfusion lung injury in 25% of patients, followed by reperfusion edema in 16%. Furthermore, the pooled incidence of perforation by guidewire, right ventricular failure and acute pulmonary embolism (APE) was 3.6%, 1.8% and 1.2%, respectively.

3.2. Outcome analysis

3.2.1. Pulmonary artery pressure (PAP)

Sixteen studies reported data on mean PAP (621 patients). Mean PAP was significantly reduced after BPA (−14.2 mm Hg [95% CI −18.9, −9.5]) (Fig. 2). Random-effects meta-regression analysis failed to significantly attribute heterogeneity in PAP to female gender (coefficient: 0.104 [95% CI −0.033, 0.242]; $p = 0.136$).

3.2.2. Pulmonary vascular resistance (PVR)

A total of 15 studies reported data on PVR (565 patients). BPA led to a significant reduction in PVR (−303.5 dyn·s/cm⁵ [95% CI −377.6, −229.4]) (Supplementary Fig. 2). Meta-regression analysis could not significantly attribute heterogeneity in PVR to female gender (coefficient: −1.423 [95% CI −4.914, 2.068]; $p = 0.424$).

3.2.3. Right atrial pressure (RAP)

Twelve studies contained adequate data on mean RAP (471 patients). Mean RAP was significantly decreased after BPA (−2.7 mm Hg [95% CI −4.1, −1.3]) (Supplementary Fig. 3). Female gender did not significantly contribute to heterogeneity seen in RAP (coefficient: −0.008 [95% CI −0.060, 0.044]; $p = 0.760$).

3.2.4. Cardiac output (CO)

Cardiac output was reported in six studies (215 patients). BPA led to a significant increase in CO (0.2 l/min [95% CI 0.0, 0.3]) (Supplementary Fig. 4).

3.2.5. 6-Minute walk distance (6-MWD)

6-MWD values were present in 12 studies (492 patients). A significant increase in 6-MWD was observed after BPA (67.3 m [95% CI 53.8, 80.8]) (Supplementary Fig. 5). Meta-regression analysis did not find female gender to significantly contribute to heterogeneity observed in 6-MWD (coefficient: 0.289 [95% CI −0.436, 1.013]; $p = 0.435$).

3.2.6. Heart rate (HR)

Seven studies reported change in HR following BPA (298 patients). HR was significantly reduced post-BPA (−6.39 bpm [95% CI −9.31, −3.47]) (Supplementary Fig. 6).

3.2.7. Oxygen saturation (SaO₂)

Oxygen saturation values were presented in 4 studies (177 patients). SaO₂ was significantly increased following BPA (3.09% [95% CI 1.03, 5.14]) (Supplementary Fig. 7).

3.2.8. Mortality

Mortality rates were reported in 12 studies with median follow-up of 9 months (range, 1–51 months). The pooled incidence of mortality was 1.9% in the short-term (≤ 1 month) and 5.7% in the long-term (> 1 month) post-BPA.

Due to the low number of studies reporting change in SV ($n = 2$), SVI ($n = 1$), systolic and diastolic blood pressure ($n = 2$), NYHA class ($n = 2$), GFR ($n = 2$) and Cr ($n = 2$) following BPA, these outcomes could not be analyzed.

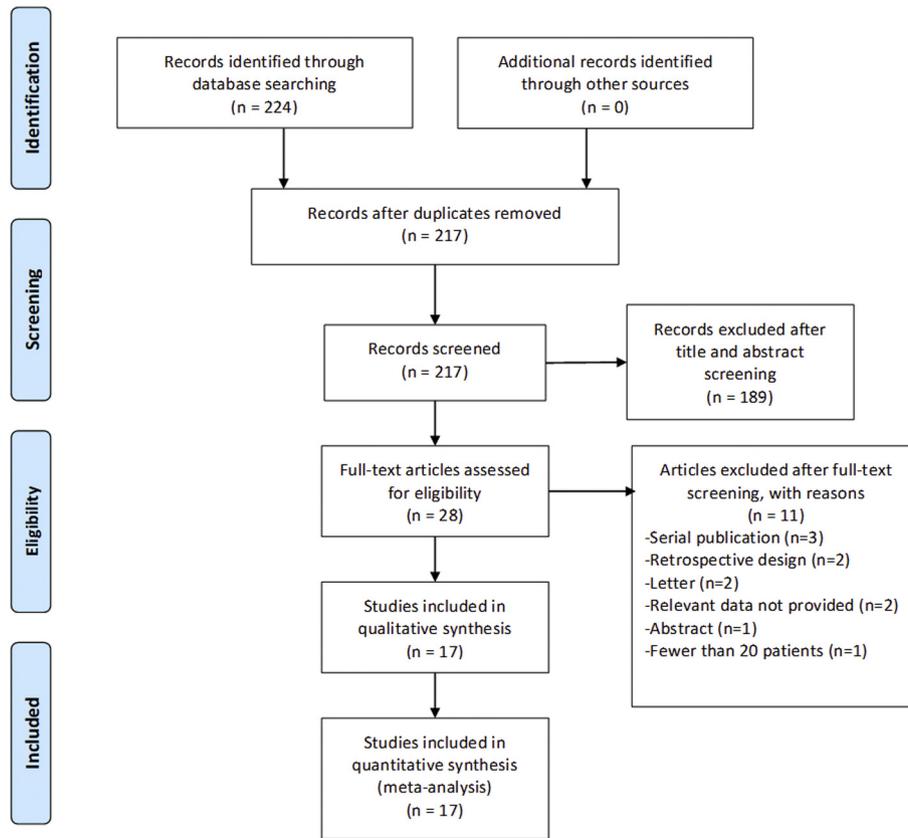


Fig. 1. PRISMA flowchart outlining the literature search process.

4. Discussion

This systematic review and meta-analysis of 670 CTEPH patients highlights significant hemodynamic improvements and overall low mortality rates following BPA. Furthermore, 6-MWD was also significantly increased following BPA, suggesting improvements in exercise capacity. This body of evidence was derived from nonrandomized noncomparative studies that evaluated patients before and after the procedure. Therefore, certainty in these estimates is modest [10]. More importantly, lack of comparative controls would prevent us

discerning with certainty whether the observed hemodynamic changes are the purely the results of BPA rather than other concomitant interventions or retrogression to the means.

Nonetheless, given the progressive natural history of CTEPH, these findings are notable as they reinforce the potential role of BPA as a viable treatment option for inoperable CTEPH. Patients with chronically elevated PVR, and hence elevated PAP, in whom pulmonary thromboendarterectomy is not technically suitable and medical therapy is ineffective, currently have no other treatment options. Percutaneous BPA may help to fill this gap, owing to its ability to reduce PVR and

Table 1
Study characteristics and patient demographics of included studies.

First author	Year of publication	Patients, n	Female, %	Mean age, years	No. of BPA sessions/patient	Mean follow-up, months	LVEF, %	Mean BMI, kg/m ²	History of smoking, %	Oxygen therapy, %	WHO functional class, I/II/III/IV
Kataoka, M [21]	2012	29	79.3	62.3	1.8	6.0	NR	NR	NR	NR	NR
Mizoguchi, H [22]	2012	68	78.0	62.2	4.0	66.0 ^a	NR	NR	NR	NR	0/0/49/19
Andreassen, A. K [23]	2013	20	50.0	60.0	18.6	51.0	NR	27.5 ± 4.7	70	NR	NR
Aoki, T [24]	2016	24	75.0	70.0	4.7	6.0 ^a	NR	NR	NR	79	0/12/11/1
Broch, K [25]	2016	26	57.7	59.0	4.0	87.0	NR	26.1 ± 4.4	65	NR	0/6/16/4
Kinutani, H [26]	2016	28	67.9	64.8	3.0	1.0	NR	NR	NR	NR	NR
Tatebe, S [27]	2016	35	74.3	63.0	3.5	15.8	NR	23.6 ± 3.9	34	75	0/33/21/1
Tsugu, T [28]	2016	26	76.9	63.0	6.0	6.0 ^a	71.9 ± 7.2	NR	NR	88	0/5/18/3
Yaoita, N [29]	2016	27	85.2	57.0	3.8	NR	NR	24.8 ± 4.5	30	NR	NR
Aoki, T [30]	2017	77	81.8	65.0	5.0	43.0	NR	NR	NR	83	4/52/18/7
Darocho, S [31]	2017	25	48.0	58.5	3.8	12.0	NR	NR	NR	NR	0/1/20/4
Kurzyna, M [32]	2017	56	50.0	58.6	3.8	24.0	NR	NR	NR	NR	NR
Moriyama, H [33]	2017	53	75.0	62.6	6.0	NR	70.7 ± 7.1	NR	NR	NR	0/11/36/6
Olsson, K. M [34]	2017	56	60.7	65.0	5.0	6.0 ^a	NR	26 ± 4	NR	NR	0/9/40/7
Yamasaki, Y [35]	2017	20	80.0	61.9	2.7	2.9	57.4 ± 7.8	NR	NR	NR	0/2/17/1
Kramm, T [36]	2018	49	NR	NR	NR	NR	NR	28.1 ± 6.5	NR	NR	1/76/182/46
Kriebbaum, S. D [37]	2018	51	54.9	63.1	5.0	6.0 ^a	60	25.7 ± 3.8	27.5	NR	0/2/31/18

Abbreviations: NR: Not Reported; BPA: Balloon Pulmonary Angioplasty, LVEF: Left Ventricular Ejection Fraction, BMI: Body Mass Index, WHO: World Health Organization.

^a After last BPA session.

Table 2
Quality assessment of included studies using Newcastle-Ottawa scale.

Study/score	Selection				Comparability		Outcome		
	S1	S2	S3	S4	C1	C2	O1	O2	O3
Andreassen (2013)			*	*	*		*	*	*
Aoki T (2016)			*	*	*		*	*	*
Aoki T (2017)			*	*	*		*	*	*
Broch K (2016)			*	*	*		*	*	*
Darocha S (2017)			*	*	*		*	*	*
Kataoka M. (2012)			*	*	*		*	*	*
Kinutani H. (2016)			*	*	*		*	*	*
Kramm T. (2018)			*	*	*		*	*	*
Kriechbaum S. D. (2018)			*	*	*		*	*	*
Kurzyna M. (2017)			*	*	*		*	*	*
Mizoguchi H. (2012)			*	*	*		*	*	*
Moriyama H (2017)			*	*	*		*	*	*
Olsson K M (2017)	*		*	*	*		*	*	*
Tatebe S. (2016)			*	*	*		*	*	*
Tsugu T. (2016)			*	*	*		*	*	*
Yamasaki Y. (2017)			*	*	*		*	*	*
Yaoita N. (2016)			*	*	*		*	*	*

S1: Representativeness of the exposed cohort; S2: Selection of the non-exposed cohort, S3: Ascertainment of exposure, S4: Demonstration that outcome of interest was not present at start of study; C1&2: Comparability of cohorts on the basis of the design or analysis; O1: Assessment of outcome, O2: Was follow-up long enough for outcomes to occur, O3: Adequacy of follow-up of cohorts.

improve mean PAP, as demonstrated in this investigation. Furthermore, reducing PAP may hinder progression to right heart failure, the most common complication of CTEPH [4]. While pulmonary thromboendarterectomy relies on a skillful surgeon to carefully dissect out and remove pulmonary thromboembolic material, the catheter-based serial dilation of lesions helps to improve distal blood flow that may lead to significant, favorable vessel remodeling that goes beyond just the simple pressing of fibrous material against the vessel wall. Reducing localized resistance allows restoring normal blood flow to the vascular bed and reducing the load on the right ventricle. Moreover, recent studies estimate a meaningful change in 6-MWD with regards to quality of life to be approximately 33 m in PAH patients [11]. While these results may not be directly applicable to CTEPH, the present analysis shows a near two-fold increase in walk distance after BPA over this minimal meaningful distance, suggesting significant quality of life improvements.

In 2001, the first complete series of BPA in consecutive non-operable CTEPH patients was reported by Feinstein et al. [12] According to the

study, BPA was associated with high rates of short-term (30-day) mortality (5.5%) and complications. Subsequently, the procedure was abandoned for nearly a decade. Recently, however, improvements not only in angioplasty technique, but also surgical expertise, have resulted in lower mortality rates than initially presumed, resulting in a resurgence of interest in BPA and multiple published studies. Our pooled incidence of mortality of 1.9% in the short-term reflects this trend. Interestingly, similar, if not higher, 30-day mortality rates have been reported with pulmonary thromboendarterectomy, ranging from 1.3% to 24% (median 8%) [13], with direct comparisons between the two procedures conforming to this finding [14]. It should be noted though that despite technical improvements in BPA over the years, the technique and indication for BPA have currently not been standardized, especially in western countries. The differences in effects of BPA among the included studies on various hemodynamic parameters are especially indicative of this problem. Ultimately, the results of large RCTs will help elucidate the true effect of BPA and potentially introduce a standardized procedure to be emulated by BPA centers worldwide.

Percutaneous BPA should only be performed after determining the patient's eligibility for pulmonary thromboendarterectomy by an experienced multidisciplinary team. Patients who carry unfavorable risk/benefit ratios for pulmonary thromboendarterectomy or those with distal, surgically inaccessible lesions may be considered for BPA [3]. Although the eligibility of pulmonary thromboendarterectomy may be immediately apparent in some patients, others have conflicting risk/benefit ratios and varying locations for their anatomical obstructions. Comparative trials should be carried out under supervision of radiologists, surgeons and interventional cardiologists to assess the safety and benefit of either pulmonary thromboendarterectomy or BPA in such borderline surgical candidates. Enrollment into such studies may pose a challenge, however, as most CTEPH centers have disproportionate expertise between pulmonary thromboendarterectomy and BPA.

Generally, a second experienced team of surgeons should be consulted regarding surgical accessibility, as the decision about operability is often subjective, and heavily influenced by the experience of the surgeon and the referral center [15]. Furthermore, standardized objective risk score, such as REVEAL risk score, to identify which BPA candidates are most likely to benefit should be developed and validated with the assistance of CTEPH registries [16]. We also planned to conduct a REVEAL risk score calculation to assess change in risk after BPA; however; this was not possible due to lack of relevant data in included studies.

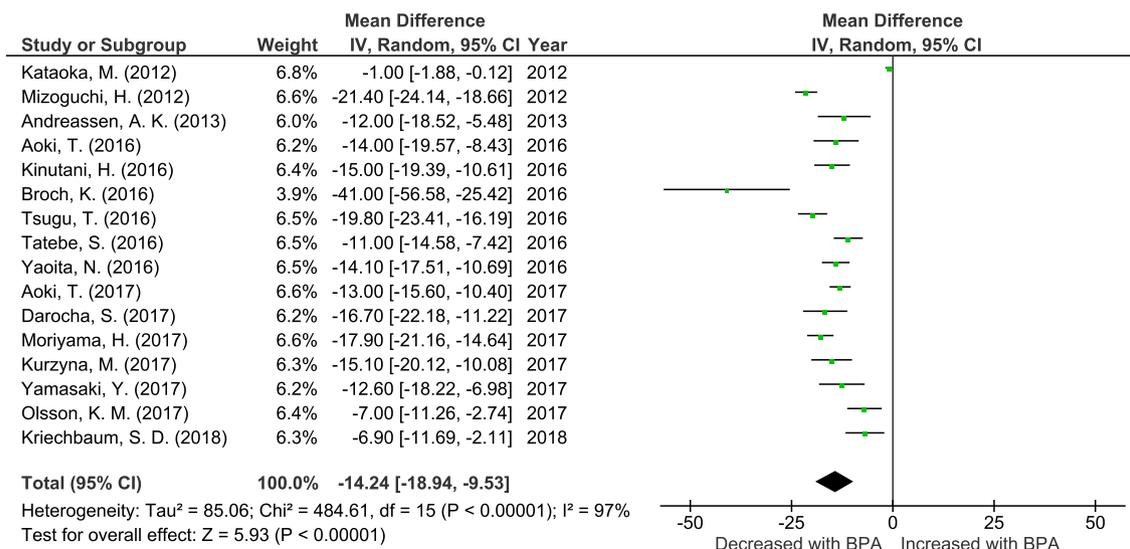


Fig. 2. Forest Plot showing change in mean pulmonary artery pressure (mm Hg) following BPA.

Preprocedural pulmonary vascular imaging can help to identify lung segments that may benefit from revascularization, thus helping to guide the intervention. More recently, imaging has also been used to classify the pulmonary vascular lesions themselves. Kawakami et al. [17] studied 500 consecutive pulmonary angioplasties consisting of a total of 1936 lesions in 97 patients. The authors identified five distinct classes of lesions, and demonstrated that subsequent outcomes and complications strongly correlated with lesion type. Imaging could identify which lesions to target with BPA, resulting in fewer complications and improved clinical outcomes.

Medical therapy in the treatment of inoperable CTEPH has been recently tested. The only currently approved drug therapy, riociguat, a soluble guanylate cyclase stimulator, has shown promising results [3,18]. Medical therapy adjunctive to BPA has scarcely been reported in the literature [19,20], and no robust data are available regarding this treatment combination. The comparative efficacy and safety of riociguat and BPA have not been investigated. However, the ongoing RACE (Riociguat Versus Balloon Pulmonary Angioplasty in Non-operable Chronic thromboembolic Pulmonary Hypertension) (ClinicalTrials.gov identifier NCT02634203) and MR BPA (Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty for chronic thromboembolic pulmonary hypertension) (UMIN Clinical Trials Registry identifier UMIN000019549) trials may provide useful insight on this matter.

4.1. Limitations

First, none of the studies included a control group. Second, most selected outcomes demonstrated significant heterogeneity, which could not be further addressed owing to lack of outcome stratification in subgroups. Especially, the effects of race and gender on outcomes could not be studied as none of the studies stratified outcomes based on these subgroups. Third, the effect of concomitant background medical therapy could not be assessed. The approximation of means and SDs from median and interquartile ranges could lead to inaccurate estimates. Some of the studies included in the analysis reported data from the same institution; therefore, it is possible the analysis might have been performed using overlapping patient data which could not be accounted for. The outcomes of change in SV, SVI, NYHA class, GFR, and Cr could not be assessed due to few studies reporting them. REVEAL risk calculation also could not be carried out due to inaccessibility of individual patient data. Lastly, the studies were small leading to imprecise estimates.

4.2. Conclusions

This systematic review and meta-analysis suggests moderate improvements in hemodynamic parameters and low mortality following BPA. Determining the true effect of BPA in inoperable CTEPH patients requires large, international, multi-center, randomized controlled trials. Until such studies are available, the results of this meta-analysis can be helpful to facilitate clinical decision making.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.02.051>.

Acknowledgements

The abstract of this study has been accepted in American Heart Association Scientific Sessions 2018 (AHA 2018).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

Grant support

None.

References

- [1] M.M. Hoeper, M.M. Madani, N. Nakanishi, B. Meyer, S. Cebotari, L.J. Rubin, Chronic thromboembolic pulmonary hypertension, *Lancet Respir. Med.* 2 (7) (2014) 573–582.
- [2] J. Pepke-Zaba, M. Delcroix, I. Lang, et al., Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry, *Circulation*. 124 (18) (2011) 1973–1981.
- [3] N. Galie, M. Humbert, J.L. Vachiery, et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), *Eur. Heart J.* 37 (1) (2016) 67–119.
- [4] M. Delcroix, I. Lang, J. Pepke-Zaba, et al., Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry, *Circulation* 133 (9) (2016) 859–871.
- [5] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *PLoS Med.* 6 (7) (2009), e1000097.
- [6] G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, Accessed date: 6 September 2018.
- [7] R. DerSimonian, R. Kacker, Random-effects model for meta-analysis of clinical trials: an update, *Contemp. Clin. Trials* 28 (2) (2007) 105–114.
- [8] Higgins JPT, S. Green (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. The Cochrane Collaboration, 2011, <http://handbook.cochrane.org>, Accessed date: 6 September 2018.
- [9] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, *Br. Med. J. (Clin. Res. Ed.)* 327 (7414) (2003) 557–560.
- [10] M. Hultcrantz, D. Rind, E.A. Akl, et al., The GRADE Working Group clarifies the construct of certainty of evidence, *J. Clin. Epidemiol.* 87 (2017) 4–13.
- [11] S.C. Mathai, M.A. Puhon, D. Lam, R.A. Wise, The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension, *Am. J. Respir. Crit. Care Med.* 186 (5) (2012) 428–433.
- [12] J.A. Feinstein, S.Z. Goldhaber, J.E. Lock, S.M. Ferndandes, M.J. Landzberg, Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension, *Circulation* 103 (1) (2001) 10–13.
- [13] M. Rahnavardi, T.D. Yan, C. Cao, M.P. Vallely, P.G. Bannon, M.K. Wilson, Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension: a systematic review, *Ann. Thorac. Cardiovasc. Surg.* 17 (5) (2011) 435–445.
- [14] Y. Taniguchi, K. Miyagawa, K. Nakayama, et al., Balloon pulmonary angioplasty: an additional treatment option to improve the prognosis of patients with chronic thromboembolic pulmonary hypertension, *EuroIntervention* 10 (4) (2014) 518–525.
- [15] M. Madani, E. Mayer, E. Fadel, D.P. Jenkins, Pulmonary endarterectomy. Patient selection, technical challenges, and outcomes, *Ann. Am. Thorac. Soc.* 13 (Suppl. 3) (2016) S240–S247.
- [16] R.L. Benza, H.W. Farber, A. Frost, et al., REVEAL risk score in patients with chronic thromboembolic pulmonary hypertension receiving riociguat, *J. Heart Lung Transplant.* 37 (7) (2018) 836–843.
- [17] T. Kawakami, A. Ogawa, K. Miyaji, et al., Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty, *Circ. Cardiovasc. Interv.* 9 (10) (2016).
- [18] H.A. Ghofrani, A.M. D'Armini, F. Grimminger, et al., Riociguat for the treatment of chronic thromboembolic pulmonary hypertension, *N. Engl. J. Med.* 369 (4) (2013) 319–329.
- [19] T. Tsugu, M. Murata, T. Kawakami, et al., Amelioration of right ventricular function after hybrid therapy with riociguat and balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension, *Int. J. Cardiol.* 221 (2016) 227–229.
- [20] S. Darocha, M. Banaszkiwicz, A. Pietrasik, et al., Sequential treatment with sildenafil and riociguat in patients with persistent or inoperable chronic thromboembolic pulmonary hypertension improves functional class and pulmonary hemodynamics, *Int. J. Cardiol.* 269 (2018) 283–288.
- [21] M. Kataoka, T. Inami, K. Hayashida, et al., Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension, *Circ. Cardiovasc. Interv.* 5 (6) (2012) 756–762.
- [22] H. Mizoguchi, A. Ogawa, M. Munemasa, H. Mikouchi, H. Ito, H. Matsubara, Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension, *Circ. Cardiovasc. Interv.* 5 (6) (2012) 748–755.
- [23] A.K. Andreassen, A. Ragnarsson, E. Gude, O. Geiran, R. Andersen, Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension, *Heart* 99 (19) (2013) 1415–1420.
- [24] T. Aoki, K. Sugimura, K. Nochioka, et al., Effects of balloon pulmonary angioplasty on oxygenation in patients with chronic thromboembolic pulmonary hypertension—importance of intrapulmonary shunt, *Circ. J.* 80 (10) (2016) 2227–2234.
- [25] K. Broch, K. Murbraech, A. Ragnarsson, et al., Echocardiographic evidence of right ventricular functional improvement after balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension, *J. Heart Lung Transplant.* 35 (1) (2016) 80–86.

- [26] H. Kinutani, T. Shinke, K. Nakayama, et al., High perfusion pressure as a predictor of reperfusion pulmonary injury after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension, *IJC Heart Vasc.* 11 (2016) 1–6.
- [27] S. Tatebe, K. Sugimura, T. Aoki, et al., Multiple beneficial effects of balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension, *Circ. J.* 80 (4) (2016) 980–988.
- [28] T. Tsugu, M. Murata, T. Kawakami, et al., Changes in right ventricular dysfunction after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension, *Am. J. Cardiol.* 118 (7) (2016) 1081–1087.
- [29] N. Yaoita, K. Satoh, T. Satoh, et al., Thrombin-activatable fibrinolysis inhibitor in chronic thromboembolic pulmonary hypertension, *Arterioscler. Thromb. Vasc. Biol.* 36 (6) (2016) 1293–1301.
- [30] T. Aoki, K. Sugimura, S. Tatebe, et al., Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: long-term effects and procedure-related complications, *Eur. Heart J.* 38 (42) (2017) 3152–3159.
- [31] S. Darocha, R. Pietura, A. Pietrasik, et al., Improvement in quality of life and hemodynamics in chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty, *Circ. J.* 81 (4) (2017) 552–557.
- [32] M. Kurzyna, S. Darocha, R. Pietura, et al., Changing the strategy of balloon pulmonary angioplasty resulted in a reduced complication rate in patients with chronic thromboembolic pulmonary hypertension. A single-centre European experience, *Kardiol. Pol.* 75 (2017) 645–654.
- [33] H. Moriyama, M. Murata, T. Tsugu, et al., The clinical value of assessing right ventricular diastolic function after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension, *Int. J. Card. Imaging.* 34 (2017) 875–882.
- [34] K.M. Olsson, C.B. Wiedenroth, J.C. Kamp, et al., Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience, *Eur. Respir. J.* 49 (6) (2017).
- [35] Y. Yamasaki, M. Nagao, K. Abe, et al., Balloon pulmonary angioplasty improves inter-ventricular dyssynchrony in patients with inoperable chronic thromboembolic pulmonary hypertension: a cardiac MR imaging study, *Int. J. Card. Imaging* 33 (2) (2017) 229–239.
- [36] T. Kramm, H. Wilkens, J. Fuge, et al., Incidence and characteristics of chronic thromboembolic pulmonary hypertension in Germany, *Clin. Res. Cardiol.* 107 (2018) 548–553.
- [37] S.D. Kriebbaum, C.B. Wiedenroth, J.S. Wolter, et al., N-terminal pro-B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension, *J. Heart Lung Transplant.* 37 (5) (2018) 639–646.