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Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: A systematic review

Nobuhiro Tanabe[a,b,*], Takashi Kawakami[c], Toru Satoh[d], Hiromi Matsubara[e], Norifumi Nakanishi[f], Hitoshi Ogino[g], Yuichi Tamura[h], Ichizo Tsujino[i], Aiko Ogawa[e], Seiichiro Sakao[b], Mari Nishizaki[j], Keiichi Ishida[k], Yasunori Ichimura[b], Masahiro Yoshida[l], Koichiro Tatsumi[b]

[a]Department of Advanced Medicine in Pulmonary Hypertension, Graduate School of Medicine, Chiba University, Chiba, Japan
[b]Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan
[c]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan
[d]Division of Cardiology Department of Medicine, Kyorin University Hospital, Mitaka, Japan
[e]Department of Clinical Science, National Hospital Organization, Okayama Medical Center, Okayama, Japan
[f]Department of Cardiovascular Medicine, Minami Osaka Hospital, Osaka, Japan
[g]Department of Cardiovascular Surgery, Tokyo Medical University, Tokyo, Japan
[h]Division of Cardiovascular Internal Medicine, International University of Health and Welfare, Mita Hospital, Tokyo, Japan
[i]First Department of Medicine, Hokkaido University Hospital, Sapporo, Japan
[j]Department of Rehabilitation, National Hospital Organization, Okayama Medical Center, Okayama, Japan
[k]Department of Cardiovascular Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan
[l]Department of Hepato-Biliary-Pancreatic and Gastrointestinal Surgery, International University of Health and Welfare, School of Medicine, Narita, Japan

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ABSTRACT

Background: Balloon pulmonary angioplasty (BPA) has been performed for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or residual pulmonary hypertension after pulmonary endarterectomy (PEA). We performed a systematic review to assess the efficacy and safety of BPA, especially compared to medical treatment or PEA.
Methods: We reviewed all studies investigating pre- and post-treatment pulmonary

Abbreviations: BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; TPR, total pulmonary vascular resistance; 6-MWD, 6-min walk distance; WHO, World Health Organization; CI, confidence intervals

*Correspondence to: Department of Advanced Medicine in Pulmonary Hypertension, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuou-ku, Chiba 260-8670, Japan.
E-mail addresses: ntanabe@faculty.chiba-u.jp (N. Tanabe), kawakami.1650@gmail.com (T. Kawakami), tsatoh2008@me.com (T. Satoh), matsubara.hiromi@gmail.com (H. Matsubara), nnakanis@hsp.ncvc.go.jp (N. Nakanishi), hogino@tokyo-med.ac.jp (H. Ogino), tamura.u1@gmail.com (Y. Tamura), itsujino-circ@umin.net (I. Tsujino), aiko-oky@umin.ac.jp (A. Ogawa), sakaos@faculty.chiba-u.jp (S. Sakao), marinishi631@gmail.com (M. Nishizaki), k-ishida@faculty.chiba-u.jp (K. Ishida), yichimura@earth.nifty.jp (Y. Ichimura), dr44da@yahoo.co.jp (M. Yoshida), tatsumi@faculty.chiba-u.jp (K. Tatsumi).

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hemodynamics, mortality, or complications from three electronic databases (PubMed, Cochrane Library, Japan Medical Abstracts Society) prior to February 2017. From 26 studies retrieved, we selected 13 studies (493 patients): the 10 most recent ones including complete data from each institution, one study of residual pulmonary hypertension, and two studies comparing BPA with medical treatment or PEA.

Results: No randomized controlled or prospective controlled studies comparing BPA with medical treatment or PEA were reported. The early mortality of BPA ranged from 0% to 14.3%; lung injury occurred in 7.0% to 31.4% (average sessions, 2.5–6.6). Mean pulmonary arterial pressure decreased from 39.4–56 to 20.9–36 mm Hg, and the 6-min walk distance increased from 191–405 to 359–501 m. The 2-year mortality of 80 patients undergoing BPA was significantly lower compared to 68 patients receiving medical treatment (1.3% vs. 13.2%); the risk ratio was 0.14 (95% confidence interval: 0.03–0.76). No significant difference was observed in the 2-year mortality between BPA ($n=97$) and PEA ($n=63$) patients.

Conclusions: This systematic review suggests that BPA improves hemodynamics, has acceptable early mortality, and may improve long-term survival compared with medical treatment in inoperable CTEPH patients.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary hypertension caused by non-resolving thromboembolism of pulmonary arteries and pulmonary vascular remodeling; right heart failure develops without effective treatment [1]. After anticoagulation for at least 3 months, the primary treatment is pulmonary endarterectomy (PEA) if the thrombi are surgically accessible [2]. Feinstein et al. reported a series of patients who underwent balloon pulmonary angioplasty (BPA) for inoperable CTEPH [3] with significant improvement in pulmonary hemodynamics; however, this treatment has not been recommended because of high pulmonary injury rates and mortality. Since 2012, several Japanese groups reported the efficacy and safety of BPA with improved techniques [4–6]. However, no controlled studies comparing survival and improvement in pulmonary hemodynamics between BPA and medical treatment or PEA have been reported. There are no previously reported systematic reviews. We conducted a systematic review to assess the efficacy and safety of BPA, focusing on survival and improvement in pulmonary hemodynamics, compared to medical treatment or PEA.

2. Methods

2.1. Literature search

We performed a systematic review using three electronic databases (PubMed, Cochrane Library, Japan Medical Abstracts Society) and searched for original articles published prior to February 2017. We performed the search using the keywords “chronic thromboembolic pulmonary hypertension” or “chronic pulmonary embolism” or “chronic pulmonary thromboembolism” or “chronic thrombo-embolic pulmonary hypertension”, and “balloon pulmonary angioplasty” or “percutaneous transluminal pulmonary angioplasty”. We manually searched relevant studies according to our selection criteria.

2.2. Selection criteria

We selected studies presenting the results of BPA (pulmonary hemodynamics, mortality, or complications) for evaluation. Reports with subgroup data were selected if the entire population data were described. Case studies, reviews, and editorials were excluded. Only human studies including an English abstract were selected.

2.3. Systematic review team

Two reviewers (N.T. and T.K.) independently searched databases using the same keywords and evaluated each study using a standard form. All data were extracted from the text, tables, and figures, including Supplemental material. The study quality including limitations of observational studies was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [7,8].

2.4. Data extraction

We extracted data for hospital mortality and 1-, 2-, 3-, and 5-year survival as primary outcomes. We also extracted data for pre- and post-treatment values of mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR) or total pulmonary vascular resistance (TPR), 6-min walk distance (6-MWD), World Health Organization (WHO) functional class, and the number of BPA sessions. The rate or number of complications, such as pulmonary injury, perforation, or dissection of the pulmonary artery, and rate of intubation or extracorporeal membrane oxygenation (ECMO), were also extracted. We compared the results between BPA and medical treatment and between BPA and PEA.

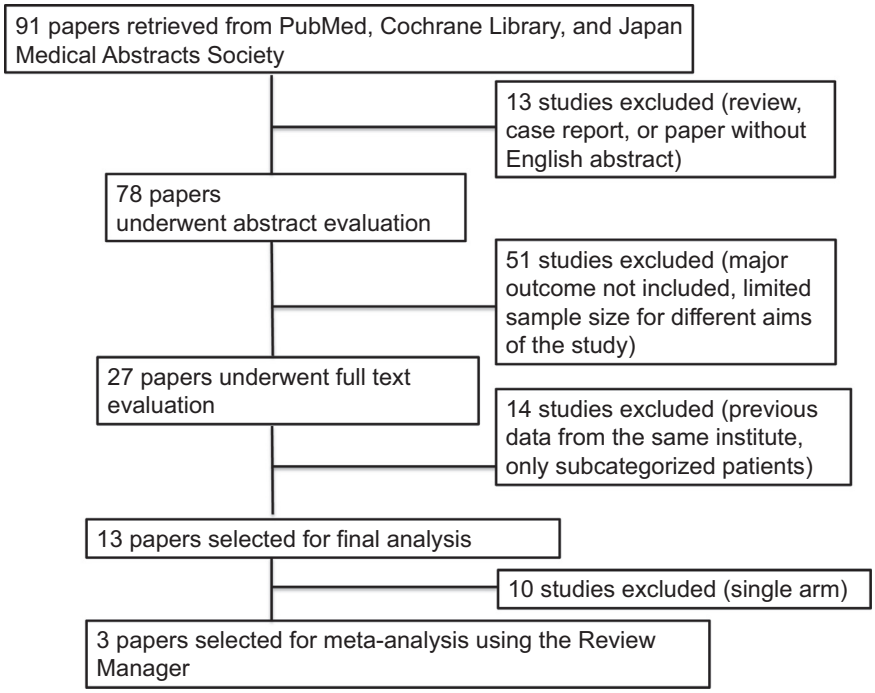

Fig. 1 – Process of study selection.

2.5. *Bias risk*

According to the GRADE evaluation, we judged the risk of bias criteria for non-randomized studies. Domains of six biases for each outcome (biases due to baseline confounding, study participant selection, departures from intended interventions, missing data, taking measurements, and selective reporting) were assessed for each paper. The risk of bias across all studies for each domain was determined. Finally, the overall assessment of the risk of bias across studies was determined [7,8].

2.6. *Quality assessment*

A quality assessment for BPA vs. medical treatment (some in PEA) was performed for each outcome according to the GRADE evaluation and included the following: the number of patients (studies), study design, limitations, inconsistency, indirectness, imprecision, and risk of publication bias [7,8].

2.7. *Statistical analysis*

The results are expressed as mean ± SD for continuous variables. Continuous variables were analyzed with the Student's *t*-test. Categorical variables were analyzed with the chi-square test. For comparisons of two treatments, the number of events was calculated from the survival rate and data from personal communications with the authors. We reported the effect measures for each outcome as the risk ratio (RR) with the related 95% confidence intervals (CI) by using Mantel-Haenszel random-effects models using the Review Manager (RevMan computer program, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A P value of <0.05 was considered statistically significant.

3. Results

3.1. *Search results*

We reviewed and screened 91 publications. Application of the selection criteria yielded 27 papers (Fig. 1, Table 1). Papers targeting biomarkers other than pulmonary hemodynamics or those compiling a number of patients from the same institute were identified.

Studies comparing BPA and medical treatment or PEA ($n=3$) [4,9,10] and those including the most recent and complete data ($n=9$) from each institute remained [11–18]. Additionally, a study that focused on residual PH was also retained [19]. Finally, 13 studies with a total number of 493 patients were included (Table 2). After the systematic review of February 2017, two large case series focusing on the benefit of BPA on long-term survival were published [20,21]; we added the results of these two studies in Tables 2–4.

3.2. *Quantity of evidence*

No randomized controlled trials (RCT) or matched controlled studies were identified. Apart from one prospective study, other studies were retrospective with some prospective components, entirely retrospective, or without design specifications. One prospective study compared the change in pulmonary hemodynamics between medical treatment and BPA following medical treatment in the same patients [4]. Two studies compared survival between the BPA group and a historical medical group or a medical group during the observational period [4,9]. Two studies compared survival between the BPA and PEA groups [9,10]. Other studies included small-sized, single-arm BPA groups. The largest series included 103 patients treated with BPA [11]. Nine of the 13 studies were from Japan. The indication for BPA

Table 1 – Twenty-seven studies screened on BPA for CTEPH.

Location	First author	Refs.	Year	No. of pts.	Indication for BPA	Description of procedure	Early Mortality	Complication	Pulmonary hemodynamics	6-MWD	WHO FC	Long term outcome
Boston, USA	Feinstein[#1]	3	2001	18	+	+	+	+	+	+	+	+
Tohoku, Japan	Sugimura[#2]	4	2012	12	+	+	+	+	+	+	+	+
	Tatebe	S1	2016	35	+	+	+	NR	+	+	+	NR
	Sato[#11]	18	2016	30	+	+	+	+	+	+	+	NR
	Aoki	S2	2016	24	+	+	+	NR	+	+	+	NR
Kyorin, Japan	Kataoka	6	2012	29	+	+	+	+	+	+	+	NR
	Inami	S3	2013	54	+	+	+	+	+	+	NR	NR
	Inami[#5]	9	2014a	68	+	+	+	+	+	+	+	+
	Inami[#6]	11	2014b	103	NR	+	+	+	+	+	NR	NR
	Yanagisawa	S4	2014	70	+ elderly	+	+	+	NR	NR	NR	NR
	Shimura[#13]	19	2015	9	+post PEA	+	+	+	+	NR	+	NR
	Sueoka	S5	2015	12	-APS only	+	+	+	+	NR	+	NR
	Inami	S6	2016	170	NR	NR	NR	NR	+	NR	NR	+
Okayama, Japan	Mizoguchi	5	2012	68	+	+	+	+	+	+	+	+
	Kawakami[#12]	12	2016	97	+	+	+	+	+	+	+	NR
Oslo, Norway	Andreassen[#3]	13	2013	20	+	+	+	+	+	NR	+	+
	Broch	S7	2016	26	NR	+	+	NR	+	NR	+	NR
Osaka, Japan	Fukui	S8	2014	20	+	+	+	+	+	+	+	NR
	Fukui[#7]	14	2015	25	+	+	+	NR	+	+	+	NR
Kobe, Japan	Taniguchi[#4]	10	2014	29	+	+	+	+	+	+	+	+
Keio, Japan	Tsugu	S9	2015	20	+	+	+	+	+	NR	+	NR
	Kimura	S10	2015	46	NR	NR	+	+	+	NR	NR	NR
	Kimura[#9]	16	2016	66	NR	+	+	+	+	NR	NR	NR
	Takei	S11	2016	59	NR	NR	+	+	+	NR	+	NR
	Tsugu	S12	2016	26			+	NR	+	+	+	NR
Madrid, Spain	Velazquez[#8]	15	2015	7	+	+	+	+	+	NR	+	NR
Warszawa, Poland	Roik[#10]	17	2016	9	+	+	+	+	+	+	+	NR

[#] from Table 2 no. S for Supplementary reference no. 6-MWD: 6-min walk distance, NR: not reported, BPA: balloon pulmonary angioplasty, PEA: pulmonary endarterectomy, APS: antiphospholipid syndrome, WHO FC: World Health Organization functional class.

Table 2 – Thirteen studies initially selected for analysis and two new studies added later.

First author Date, [Study#]	Study period	No. of pts.	Indication for BPA	Average no of procedures	30-day mortality	2-year Survival	Decrease in mPAP (mmHg)	Decrease in PVR (WU)	6-MWD Improvement (m)	WHO FC improvement
Feinstein, 2001 [#1]	1994–1999	18	Inaccessible comorbidity	2.6/patient	5.6%	89%	42±12 to 33±10*	2 2±9 to 17±8* (TPR)	191–454*	3.3 to 1.8*
Sugimura, 2012 [#2]	2009–2011	12	Distal 10 post PEA 2	5/patient	0%	100%	43.2±9.5 to 24.8±4.9*	8.4±3.0 to 3.9±0.9*	340±112 to 441±76*	2.6 to 2.0*
Andreassen, 2013 [#3]	2003–2011	20	Inaccessible 16, others 3, post PEA 1	3.7/patient	10%	85%	45±11 to 33±10*	8.8±4.0 5.9±3.6*	NR	3.0 to 1.9*
Taniguchi, 2014 [#4]	2011–2013	29	Inaccessible 13, other 14 post PEA 2	3/patient	3.5%	93%	39.4±6.9 to 21.3±5.6*	9.5±3.9 to 3.6±1.6*	295±95 to 397±117*	3.2 to 1.7*
Inami, 2014a [#5]	2009–2013	68	Inaccessible other	2.5/patient	1.5%	98.5%	41.9±11.8 to 25.0±6.1*	11.4±5.3 to 6.2±2.6*(TPR)	349±130 to 424±111*	2.9 to? * figure only
Inami, 2014b [#6]	2009–2013	103	NR	Median 3.5 IQR (2 to 4) /patient	0.97%	99%	Medan 41 range (34–47) to 21(18–28)*	Median 8.7 range (6.1–13.3) to 2.7(2.0–4.2)*	Median 360 range (281–430) to 420 (350–510)*	NR
Fukui, 2015 [#7]	NR	25	Inoperable	3.6/patient	0%	NR	35.8±10.3 to 23.0±5.1*	11.1±4.4* to 6.3±2.1*(TPR)	405±111 to 501±109*	2.6 to 2.1*
Veiazquez, 2015 [#8]	2013–2015	7	Inaccessible other	3/patient	14.3%	NR	56±17 to 36±10*	11.8±4 to 6.1±2.2*	NR	3.8 to 2.3*
Kimura, 2016 [#9]	2012–2015	66	NR	6.6/patient	0%	NR	39.2±10.5 to 20.9±5.4*	9.5±6.8 to 3.8±1.8*	NR	NR
Roik, 2016 [#10]	2014-2015	9	Distal	3/patient	0%	NR	Median 40 range (32–54) to 34.5 (29–42)*	Median 9.1 range (3.7–14.4) to 4.8(2.3–9.9)*	Median 304 range (135–450)* to 384 (205–530)*	3.3 to 2.2*
Sato, 2016 [#11]	2009–2015	30	Inoperable	5.1/patient	0%	NR	40.8±23.2 to 23.2±4.94*	9.3±4.2 to 3.4±1.4*	330±169 to 467±114*	3 to?*
Kawakami, 2016 [#12]	2004-2012	97	Inaccessible 87 post PEA 1 other 9	5.2/patient	1%(in hospital 4.1%)	NR	45.1±10.8 to 23.3±6.4*	12.0±5.7 to 3.9±1.9*	276±123 to 359±92*	3.3 to 1.9*
Shimura, 2015 [#13]	2009-2014	9	post PEA	4.9/patient	0%	NR	Median 43 Q1-Q3 (30–52)* to 26 (21–29)*	Median 8.1 Q1-Q3 (6.1–12.3) to 4.1 (2.4–4.8)*	NR	2.8 to 1.2
Ogawa, 2017 Ref. [20]	2004–2013	308	Inaccessible 234 Post PEA 14 Accessible 60 (Refusal of PEA 42, Unfavorable risk/benefit ratio 18)	Median 4/ patient	2.6%	96.8%	43.2±1 1.0 to 24.3±6.4*	10.7±5.6 to 4.5±2.8*	318±122 to 401±105*	Median 3 to 2*
Aoki, 2017 Ref. [21]	2009–2016	84	Inoperable	5.0/patient	0%	98.4%	38±10 to 25±6*	7.3±3.2 to 3.8±1.0*	380±138 to 486±112*	2.4 to?

Mean±SD unless otherwise stated. Q1–3: first and third quartiles, 6-MWD: 6-min walk distance, NR: not reported, PEA: pulmonary endarterectomy, mPAP: mean pulmonary arterial pressure, PVR: pulmonary vascular resistance, TPR: total pulmonary vascular resistance.

* $p<0.05$.

Table 3 – Comparison of efficacy between BPA and medical treatment or PEA.

First author Date, [Study#]	No. of pts.	mPAP Pre (mm Hg)	mPAP post (mm Hg)	PVR pre (WU)	PVR post (WU)	6-MWD pre (m)	6-MWD post (m)	WHO FC pre (mean value)	WHO FC post (mean value)
Sugimura, 2012 [#2]	BPA 12	43.2±9.5	24.8±4.9*	8.4±3.0	3.9±0.9*	340±112	441±76*	2.6	2.0*
	Control (the same pts. before BPA) 12	47.8±11.6	43.2±9.5	12.1±6.3	8.4±3.0*	350±105	340±112	2.9	2.6
	Control (medical) Historical 39	43.4±11.5	NR	10.6±4.9	NR	288±157	NR	2.5	NR
Inami, 2014 [#5]	BPA 68	41.9±11.8	25.0±6.1*	11.4±5.3 (TPR)	6.2±2.6* (TPR)	349 ± 130	424±111*	2.9	Figure only*
	Control (medical) 29	38.4±9.7	33.8±11.9	12.7±8.1 (TPR)	9.3±7.7 (TPR)	NR	NR	2.5	NR
	Control PEA 39	53.1*	27.9*	17.5	7.5*	326±116	353±93	3.2	Figure only*
Taniguchi, 2014 [#4]	BPA	39.4±6.9*	21.3±5.6*	9.5±3.9*	3.6±1.6*	295±95*	397±117*	3.2	1.7*
	Control PEA	44.4±11.0*	21.6±6.7*	9.8±3.5*	3.2±1.6*	NR	NR	3.2	1.5*
Aoki, 2017 Ref. [21]	BPA 77	38±10	25±6*	7.3±3.2	3.8±1.0*	380±138	486±112*	2.4	?
	Control (the same pts. before BPA) 77	41±19	38±10*	10±4.6	7.3±3.2*	320±136	380±138*	?	2.4
	Control (medical) Historical 20	41±8	NR	10±4.5	NR	280±166	NR	2.9	NR

Mean±SD. [#] from Table 2 no. NR: not reported, PEA: pulmonary endarterectomy, mPAP: mean pulmonary arterial pressure, PVR: pulmonary vascular resistance, TPR: total pulmonary vascular resistance, 6-MWD: 6-min walk distance, WHO FC: World Health Organization functional class.
* $p<0.05$.

Table 4 – Complications of BPA.

First author, Date [Study #]	Pulmonary artery perforation	Pulmonary artery dissection	Lung injury	Hemoptysis	ECMO	Intubation	NPPV
Feinstein, 2001 [#1]	1/18 (5.6%) (/pt.)	NR	11/18 (61.1%) (/pt.)	NR	NR	3/18 (16.7%) (/pt.)	NR
Sugimura, 2012 [#2]	0	0	NR	6/12 (50.0%) (/pt.)	0	0	6/12 (50.0%) (/pt.)
Andreassen, 2013 [#3]	NR	NR	7/20 (35.0%)(/pt.)	NR	1	1	NR
Taniguchi, 2014 [#4]	4/86 (4.7%)	0	27/86 (31.4%)	27/86 (31.4%)	0	0	58.1% (recent cases)
Inami, 2014a [#5]	0.9%	2.3%	15/213 (7.0%)	5.6%	NR	NR	NR
Inami, 2014b [#6]	28/350 (8.0%)	7/350 (2.0%)	79/350 (22.6%)	NR	NR	NR	NR
Fukui, 2015 [#7]	NR	NR	NR	NR	0	0	NR
Veiazquez, 2015 [#8]	0/27	NR	2/7 (28.6%) (/pt.)	NR	1/7 (14.2%) (/pt.)	1/7 (14.2%) (/pt.)	NR
Kimura, 2016 [#9]	NR	NR	NR	27/446 (6.1%)	0	0	5/446(1.1%)
Roik, 2016 [#10]	0	0	2/27 (7.4%) (grade >2)	NR	0	0	0
Sato, 2016 [#11]	NR	NR	NR	20/152 (13.2%)	0	0	NR
Kawakami, 2016 [#12]	91/1936 (4.7%)/lesion	16/1936 (0.83%)/lesion	130/500 (26%) (65/97) (67.0%)(/pt.)	98/500 (19.6%)	7/500 (1.4%)	10/500 (2.0%) (10/97) (10.3%)(/pt.)	NR
Shimura, 2015 [#13]	1/44 (2.3%)	0	1/44 (2.3%)	1/44 (2.3%)	0	0	1/44 (2.3%)
Ogawa, 2017 Ref. [20]	41/1408 (2.9%)	6/1408 (0.4%)	251/1408 (17.8%)	197/1408 (14%)	9/308 (2.9%) (/pt.)	17/308 (5.5%)(/pt.)	NR
Aoki, 2017 Ref. [21]	0	30/424 (7%)	NR	60/424 (14%)	0	1/424 (0.2%)	33/424 (8%)

Expressed as no./session unless otherwise stated. ECMO: extracorporeal membrane oxygenation, NPPV: non-invasive positive pressure ventilation, pt.: patient NR: not reported.

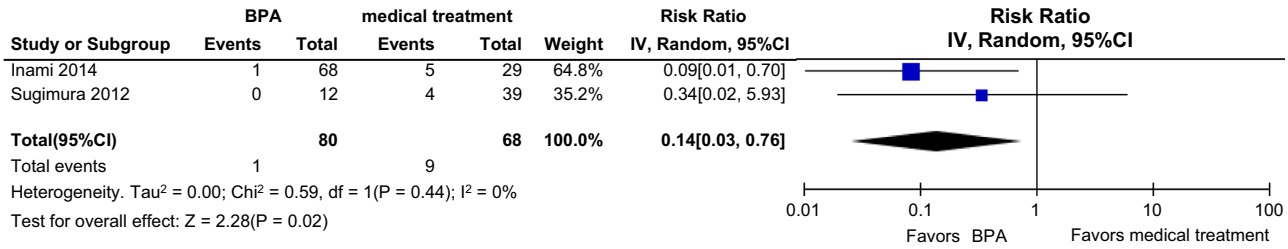

Fig. 2 – Comparison of two-year mortality between the BPA and medical treatment groups. The two-year mortality rate in the BPA group was significantly lower than in the medical treatment group (1.3% vs. 13.2%, respectively; risk ratio (RR), 0.14 [95% CI 0.03–0.76], $p=0.028$).

was described in 11 studies. The average number of sessions for BPA treatment ranged from 2.5 to 6.6. Short-term mortality was reported in all studies. Survival for more than 2 years was reported in six studies. Additionally, 30-day mortality from one study [12] and 2-year mortality of the medical group in two studies [4,9] were confirmed by personal communication.

3.3. *Mortality assessment*

3.3.1. *Evidence*

Mortality within 30 days after BPA ranged from 0% to 14.3% (Table 2). Six studies reported 2-year survival from 89% to 100%. The 2-year mortality rate in the BPA group ($n=80$) was significantly lower than in the medical treatment group ($n=68$) in 2 studies (#2, #5) (1.3% vs. 13.2%, respectively; RR, 0.14 [95% CI, 0.03–0.76], $p=0.028$) (Fig. 2). No significant difference in the 2-year mortality rate was observed between the BPA ($n=97$) and PEA groups ($n=63$) during a similar period in two studies (#2, #4) (2.1% vs. 4.8%, respectively; RR 0.74 [95% CI, 0.16–3.48], $p=0.7$) (Fig. 3).

3.3.2. *Risk of bias and quality assessment*

For baseline confounding and selection, a single arm from interventional studies, except studies # 2, 4, and 5, were included (Table S1-a). Study #4 was compared with operable cases. Studies #2 and 5 were compared with some historical controls. Studies # 5, 6, and 9 may have included operable patients. Patients were aware of BPA in all studies. A serious risk of bias was identified. In the quality assessment of BPA vs. medical treatment, serious limitations described above relating to non-RCTs were observed: very serious indirectness for the BPA vs. PEA study and possible publication bias (Table 5).

3.4. *Improvement in pulmonary hemodynamics*

3.4.1. *Evidence*

The mPAP and PVR (or TPR) decreased significantly in all studies. Study #2 reported that vasodilators did not reduce mPAP significantly; it decreased significantly after BPA (43.2 ± 9.5 to 24.8 ± 4.9 mmHg) (Table 3). Study #5 reported that pulmonary hemodynamics did not improve significantly after medical therapy in 17 of 29 patients (Table 3), while mPAP and TPR improved significantly after BPA during the observational period. The mPAP and TPR improved significantly after PEA. Study #4 reported that the mPAP and PVR improved significantly after BPA and PEA during the observational period (Table 3). Study #13 revealed that the mPAP and PVR improved significantly even in patients with residual PH after PEA (Table 2).

3.4.2. *Risk of bias and quality assessment*

A similar risk of bias for mortality was observed (Table S1-b, c). Additionally, study #2 was compared with data after medical treatment in the same patients. The follow-up period for measurement varied between the BPA and medical groups. A serious risk of bias was identified. In the quality assessment of BPA vs. medical treatment, serious limitations described above relating to non-RCTs were observed: serious indirectness for the study of BPA vs. medical treatment in the same patients, very serious indirectness for the BPA vs. PEA study, serious imprecision using TPVR instead of PVR, and possible publication bias (Table 5).

3.5. *Improvement in 6-MWD*

3.5.1. *Evidence*

Nine studies compared the 6-MWD pre- and post-PEA, with significant improvement seen in all (191–405 m to 359–501 m) (Table 2). Study #2 reported that vasodilators did not improve the 6-MWD significantly in 12 patients, while the 6-MWD improved significantly after BPA (Table 3). Study #5 reported that the 6-MWD did not improve after PEA, while it improved significantly after BPA.

3.5.2. *Risk of bias and quality assessment*

A similar risk of bias for pulmonary hemodynamics was observed (Table S1-d). In the quality assessment of BPA vs. medical treatment, serious limitations described above relating to non-RCTs were observed: serious indirectness for the study of BPA vs. medical treatment in the same patients, very serious indirectness for the BPA vs. PEA study, serious imprecision due to small patient numbers, and possible publication bias (Table 5).

3.6. *Improvement in WHO functional class*

3.6.1. *Evidence*

Ten studies compared the WHO functional class pre- and post-BPA and reported significant improvement after BPA in all studies (Tables 2 and 3). Similarly, two studies showed

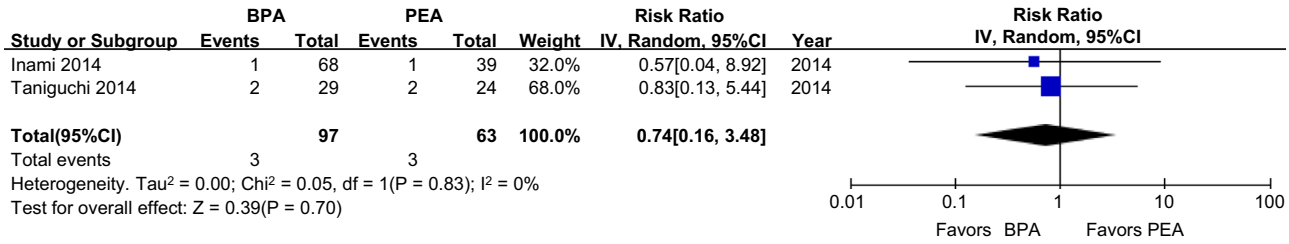

Fig. 3 – Comparison of two-year mortality between the BPA and PEA groups. No significant difference in the 2-year mortality rate was observed between groups (2.1% vs. 4.8%, respectively; RR, 0.74 [95% CI 0.16–3.48], $p=0.7$).

Table 5 – Quality assessment of studies: BPA vs. medical treatment.

Quality assessment							
No. of studies	Cases/control	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias
Outcome 1 Decreased 2-year mortality (30 days mortality*)							
2	80/68	Non RCT	Serious	Not relevant	Not relevant	Not relevant	Likely
2	97/63[a]	Non RCT	Serious	Not relevant	Very serious	Not relevant	Likely
10*	384//NA	Non RCT	Serious	Not relevant	Not relevant	Not relevant	Likely
Outcome 2 Improvement in mPAP							
2	80/41	Non RCT	Serious	Not relevant	Serious	Serious	Likely
2	97/63[a]	Non RCT	Serious	Not relevant	Very serious	Serious	Likely
10	384/NA	Non RCT	Serious	Not relevant	Not relevant	Serious	Likely
Outcome 3 Improvement in PVR							
2	80/41	Non RCT	Serious	Not relevant	Serious	Serious	Likely
2	97/63[a]	Non RCT	Serious	Not relevant	Very serious	Serious	Likely
10	384/NA	Non RCT	Serious	Not relevant	Not relevant	Serious	Likely
Outcome 4 Improvement in 6-MWD							
1	12/12	Non RCT	Serious	Not relevant	Serious	Serious	Likely
1	45/11[a]	Non RCT	Serious	Not relevant	Very serious	Serious	Likely
7	311/NA	Non RCT	Serious	Not relevant	Not relevant	Serious	Likely
Outcome 5 Improvement in WHO functional class							
1	12/12	Non RCT	Serious	Serious	Very serious	Serious	Likely
2	97/63[a]	Non RCT	Serious	Serious	Very serious	Serious	Likely
7	206/NA	Non RCT	Serious	Not relevant	Not relevant	Serious	Likely
Outcome 6 Comorbidity							
12	468/NA	Non RCT	Serious	Not relevant	Very serious	Serious	Likely

[a] PEA for control. BPA: balloon pulmonary angioplasty; RCT: randomized controlled trial; 6-MWD: 6-min walk distance; NA: not available.

significant improvement in the WHO functional class after PEA (Table 3).

3.6.2. *Risk of bias and quality assessment*

A similar risk of bias for pulmonary hemodynamics was observed, while study #4 had missing data after medical treatment (Table S1-e). In the quality assessment for BPA vs. medical treatment, serious limitations described above relating to non-RCTs were observed: very serious indirectness for the study of BPA vs. medical treatment in the same patients without statistical analysis, very serious indirectness for the BPA vs. PEA study, serious imprecision due to small patient numbers, and possible publication bias.

3.7. *Complications*

3.7.1. *Evidence*

The average number of sessions varied from 2.5 to 6.6. Among eight studies reporting the number of BPA complications per session for 1828 sessions (#4–6, 9–13), lung injury, previously expressed as reperfusion pulmonary injury, occurred in 7.0–31.4%, hemoptysis in 5.6–19.6%, and pulmonary artery perforation in 0–8.0% (Table 4). RPI occurred in 20 of 45 patients (44.4%) in 3 studies. Severe complications requiring tracheal intubation occurred in 15 patients, and 9 patients needed ECMO.

3.7.2. *Risk of bias and quality assessment*

A similar risk of bias for pulmonary hemodynamics was observed (Table S1-f). No complication from medical treatment was included. In the quality assessment for BPA vs. medical treatment, serious limitations described above relating to non-RCTs were observed: very serious indirectness for the BPA vs. PEA study and possible publication bias since there were no reports from the medical therapy group.

4. Discussion

This systematic review included the 10 most recent studies from different centers and 3 studies comparing BPA with medical treatment or PEA. No RCTs were found in our

literature search. In the two observational cohort studies, survival was better with BPA compared to those who underwent medical treatment alone. BPA resulted in improved hemodynamics, the 6-MWD, and the WHO functional class and resulted in lower 30-day mortality, although complications such as RPI and hemoptysis were a concern. This is the first systematic review showing a benefit with BPA in CTEPH.

Several issues require discussion. First, the 30-day mortality ranged from 0% to 14.3%. In the high-volume center treating more than 50 patients, 30-day mortality was less than 1.5%, although all centers were Japanese. Kawakami showed that the success rate was high with a lower complication rate in ring-like stenosis and web lesions, and tortuous lesions were associated with a high complication rate. The BPA technique varied among institutions, including the use of intravascular ultrasound, optical coherence tomography, pressure wires, and different balloon sizes. There is a learning curve prior to the safe and successful performance of BPA. Expertise and consideration of lesion classification are important for balancing the benefits versus harm resulting from BPA.

Second, indications for BPA in most patients were either inoperable lesions due to inaccessibility for PEA or comorbidity; however, one study did not mention the indication. The Japanese statement suggests that BPA is basically indicated for patients who are ineligible for PEA and do not respond sufficiently to medical therapy [22]. However, there were several marginal candidates for BPA because few patients were treated by PEA in Japan. Some operable patients in Western countries may be treated by BPA, and in this population, BPA may also improve survival similar to PEA.

Third, the 2-year survival in the BPA group was better than that of the medically treated group, although controls were either historical or non-BPA candidates in the same institution. However, the 2-year survival of patients in a European registry who were mainly treated by pulmonary vasodilators was 79% [22], which was lower than the results with BPA (85–100%). It is likely that BPA improved survival, although confirmation by a prospective study is necessary.

Fourth, BPA treatment requires several procedures after hospital admission, with high treatment costs. Recently, Ogawa et al. showed that the use of supplemental oxygen and PAH-targeted drugs was significantly reduced after BPA from the analysis of a multi-institutional registry [20]. Aoki et al. reported that while 96% of patients received vasodilators before BPA, only 41% of patients needed vasodilators after BPA [21]. These data may support reduced cost of care after BPA. No studies evaluated the cost-benefit ratio following BPA, but most patients had improved WHO functional class and could work and live a near-normal life. Thus, BPA may reduce the overall cost to society.

Fifth, in this review, BPA was performed in a small number of patients who had residual pulmonary hypertension. One report that combined data from Kyorin and Keio Universities revealed that BPA also was useful for these patients [19]. A further large study targeting residual pulmonary hypertension after PEA is necessary.

Sixth, after the systematic review was performed in February 2017, two large case-series reported on the benefit of BPA on long-term survival. Ogawa, et al. reported the results from a multicenter registry of BPA in Japan, although most of these patients may have been already included in the current systematic review [20]. They showed improved pulmonary hemodynamics and 6-MWD after BPA with an acceptably low complication rate in 308 patients (Tables 2 and 4); the overall survival at 3 years was 94.5%. Aoki et al. also reported significantly better survival in the BPA group compared to a historical control group (5-year survival 98.4 vs. 77.5%, $p<0.02$) [21]. They also showed a significantly better survival in the BPA group compared with a historical control group even after propensity score matching with age, pulmonary hemodynamics, and the use of medication.

Seventh, a randomized controlled study of riociguat showed significant improvement in 6-MWD and PVR, resulting in fair survival [23,24]. Riociguat has been available since 2014 in Japan. In this systematic review, we compared the benefit of BPA on pulmonary hemodynamics and the 6-MWD with medical treatment between 2009 and 2013. Thus, patients treated with riociguat were not included. Recently, Aoki et al. reported significantly improved pulmonary hemodynamics and the 6-MWD with medical treatment (17% of patients received riociguat) before BPA [21]. Further improvement in pulmonary hemodynamics and the 6-MWD were observed in the same patients after BPA. Thus, medical treatment with or without BPA may be useful.

Finally, this study has several limitations; most of the bias involved has already been described in the results section. With non-RCTs, baseline confounding and selection bias are serious problems. Most of the studies involved a single arm, and control subjects were either historical or medically treated patients excluded from BPA. Besides, only successful cases from expert centers may be reported, leading to bias.

5. Conclusion

This systematic review suggests that BPA improves hemodynamics with acceptable early mortality and may improve long-term survival compared with medical treatment in inoperable CTEPH patients.

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Conflict of interest

The authors have no conflicts of interest to declare for this article.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.resinv.2018.03.004.

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