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RESEARCH LETTER

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Balloon pulmonary angioplasty for patients with chronic thromboembolic pulmonary hypertension previously operated by pulmonary endarterectomy

Asger Andersen[1] | **Jacob Valentin Hansen**[1] | **Simone Juel Dragsbaek**[1] | **Michael Maeng**[1] | **Mads Jønsson Andersen**[1] | **Gratien Andersen**[2] | **Søren Mellemjkaer**[1] | **Lars Bo Ilkjær**[3] | **Jens Erik Nielsen-Kudsk**[1]

[1]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Radiology, Aarhus University Hospital, Aarhus, Denmark

[3]Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark

Correspondence
Asger Andersen, Department of Cardiology, Aarhus University Hospital, Palle Juul Jensens Boulevard 99, DK-8200, Aarhus, Denmark.
Email: asger.andersen@clin.au.dk

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Abstract

Balloon pulmonary angioplasty improved hemodynamics, walking distance, and World Health Organization functional class in patients with chronic thromboembolic pulmonary hypertension not eligible for pulmonary endarterectomy (Non-PEA) and patients with persistent pulmonary hypertension after PEA (PEA). More mild complications were observed in PEA- compared to Non-PEA.

KEYWORDS

balloon pulmonary angioplasty, chronic thromboembolic pulmonary hypertension, pulmonary embolism, pulmonary hypertension

INTRODUCTION

Balloon pulmonary angioplasty (BPA) improves symptoms, exercise capacity and hemodynamics in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[1–10] A subset of patients are treated with BPA due to persistent pulmonary hypertension after surgical pulmonary endarterectomy (PEA), but the experience with BPA in such patients is sparse with only few reports on efficacy and safety.[6,8,11]

In this research letter we report the BPA experience from Denmark including our results from CTEPH patients with prior PEA.

METHODS

A retrospective cohort study of patients diagnosed with CTEPH who completed a series of BPA procedures at the Danish CTEPH center, Aarhus University Hospital from September 2nd, 2015, till December 31st, 2020 ($n = 59$). PEA has been performed in our center since 1994[12] as first line treatment in technically operable patients with a favorable risk/benefit ratio. BPA was done as described by others[5] and continued until mPAP was <25 mmHg (reached in 2 patients from the Non-PEA group) or all accessible lesions were treated. Follow-up was done at 3–6 months after last BPA or at the last BPA procedure if

follow-up data was unavailable for this analysis ($n = 7$, for these patients 6-min walking distance was not available). No changes in PAH targeted therapy were instituted from baseline (1st BPA session) to follow-up. Baseline characteristics and survival data are for the total cohort ($n = 59$) whereas follow-up data (Table 1) are from patients with available hemodynamic follow-up data ($n = 45$). The analysis was done for the total cohort (All $n = 45$), patients previously operated by PEA ($n = 18$) and patients deemed inoperable by PEA ($n = 27$). Complications were registered as mild, moderate, severe, or fatal in line with previous BPA reports.[5]

STATISTICS

Data were analyzed using GraphPad Prism version 7 (GraphPad Software). Continuous variables are presented as mean ± standard deviation (*SD*) if normally distributed or median and interquartile range if data were not normally distributed. Comparison of continuous variables was done with students *t* test if normally distributed and nonparametric tests if not normally distributed. Categorical values were presented as numbers and percentages. The Chi-square test for independence or Fisher's exact test was used to compare categorical values. For comparison between groups a nonpaired test was used, whereas a paired design was used for comparison within a group. To estimate overall survival, we used the Kaplan–Meier method with the date of first BPA session as starting point and cut-off at December 31st 2020. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Patients were primarily female (63%) with a mean age of 70 ± 11 years and most in WHO functional class 3 (78%) with a 6-min walking distance of 339 ± 137 m. The patients had impaired lung function (FEV1/FVC of 0.75 [0.69–0.75]) and a large proportion had a history of VTE (75%). Reason for surgical turn-down were technical inoperability (22%), high surgical risk (36%) PEA refusal (8%) or previous PEA (34%). Most patients were treated with PAH targeted therapy: PDE5 inhibitors (41%), sGC stimulators (20%) and endothelin receptor antagonists (12%). The PEA group had a longer time from CTEPH diagnosis to 1st BPA procedure (9 [1–18] vs. 0 (0–2) years, $p < 0.0001$), worse lung function evaluated by FEV1/FVC (0.66 [0.57–0.71] vs. 0.72 [0.64–0.77] $p = 0.05$) (possible explanation being previous PEA[13]), and more PEA patients were on PAH targeted therapy than Non-PEA

TABLE 1 Baseline patient characteristics and follow-up data after balloon pulmonary angioplasty

	All ($n = 45$)				Non-PEA ($n = 27$)				PEA ($n = 18$)			
Variable	**Baseline**	**Follow-up**	**Δ Change**	***p* value***	**Baseline**	**Follow-up**	**Δ Change**	***p* value***	**Baseline**	**Follow-up**	**Δ Change**	***p* value^**
mPAP (mmHg)	44.7 ± 9.7	35.9 ± 9.1	8.8 ± 8.9	<0.0001	43.4 ± 8.5	35.4 ± 9.7	8.0 ± 9.1	0.0002	46.7 ± 10.8	36.7 ± 8.2	10.06 ± 8.9	<0.0001	0.451
PAWP (mmHg)	10.2 ± 3.8	10.6 ± 3.4	0.9 ± 3.8	0.392	9.8 ± 4.0	10.7 ± 3.9	−0.9 ± 3.8	0.755	10.7 ± 3.4	11.5 ± 3.1	0.94 ± 3.8	0.331	0.145
CO (L/min)	4.04 ± 1.01	4.67 ± 1.23	0.63 ± 1.13	0.0004	4.10 ± 1.04	4.82 ± 1.26	0.71 ± 1.30	0.008	3.94 ± 0.97	4.46 ± 0.63	0.51 ± 0.81	0.016	0.573
PVR (dynes-sek/cm^5)	750 ± 364	461 ± 220	289 ± 304	<0.0001	739 ± 418	443 ± 203	296 ± 352	<0.0001	766 ± 275	488 ± 247	278 ± 222	<0.0001	0.853
6 MWD (m)	340 ± 130	410 ± 101	72 ± 96	0.0001	325 ± 140	418 ± 99	93 ± 111	0.003	360 ± 118	402 ± 107	43 ± 59	0.022	0.155
NT-proBNP (ng/L)	1511 ± 1813	572 ± 656	939 ± 1665	<0.0001	1556 ± 2037	384 ± 358	1220 ± 1878	<0.0001	1447 ± 1483	844 ± 877	603 ± 1318	0.048	0.239
WHO FC 1/2/3/4 (%)	0/27/70/3	27/52/21/0	0.8 ± 0.4	<0.0001	0/32/64/5	27/59/14/0	0.81 ± 0.6	<0.0001	0/18/82/0	27/36/36/0	0.92 ± 0.51	<0.0001	0.59

Note: Unless otherwise stated, results are mean ± standard deviation; * is *p* value compare to baseline within group and ^ is *p* value comparing PEA versus non-PEA.

Abbreviations: CO, cardiac output; mPAP, mean pulmonary artery pressure; 6MWD, 6-mins walking distance; Non-PEA, nonoperable for other reasons that PEA; NT-proBNP, N-terminal pro Brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class.

(95% vs. 66%, $p = 0.001$). Detailed baseline characteristics are available in Table S1, but data on surgical clearance is unfortunately not available.

Patients received a mean of 3.3 ± 1.5 BPA session with a trend towards more sessions in the PEA group (3.7 ± 1.2 vs. 3.1 ± 1.2, $p = 0.07$). We treated 2.6 ± 0.94 (PEA 2.5 ± 0.90 vs. Non-PEA 2.4 ± 0.84, $p = 0.60$) segments and 4.4 ± 1.4 lesions (PEA 4.1 ± 1.2 vs. Non-PEA 3.8 ± 0.7, $p = 0.24$) per session. We primarily treated web lesions (83%) using a mean balloon diameter of 3.26 ± 1.15 mm with fewer web lesions treated in PEA compared to Non-PEA (74% vs. 89%, $p = 0.0002$). More sub-occluded lesions were treated in the PEA group (13% vs. 4%, $p = 0.002$) with a slightly larger balloon diameter in PEA compared to the Non-PEA group (3.43 ± 1.25 vs. 3.15 ± 1.04 mm, $p = 0.014$). Details on treated segments are available in Table S2

The effects of BPA treatment for the cohort are illustrated in Table 1. Survival at 1, 2, and 3 years was 93%, 91% and 87% for the total cohort 100%, 94% and 94% for the PEA group and 89%, 89% and 83% for the Non-PEA group.

Complications occurred in 17% of BPA procedures with mild complications in 9% and moderate complications in 7% of the procedures. Severe complications requiring intensive care unit treatment occurred in 1% and we had one procedure related death: a 79-year-old woman with prior PEA and severe PH (mPAP 55 and PVR 1280 dynes-sek/cm^5) died in-hospital due to lung injury. There were more complications in PEA compared to Non-PEA (26% vs. 12%, $p = 0.02$) with more mild complications in the PEA group (15% vs. 5%, $p = 0.03$) and a trend towards more wire perforations (12% vs. 6%, $p = 0.18$) and lung injury (12% vs. 5%, $p = 0.09$). There was no statistically significant difference between the PEA and Non-PEA cohorts for moderate (10% vs. 5%, $p = 0.25$) or severe complications (1% vs 2%, $p = 0.68$). Details on complications are in Table S3.

DISCUSSION

BPA improved hemodynamics, walking distance, and WHO functional class in Non-PEA and PEA patients. We observed more mild complications in PEA-compared to Non-PEA suggesting a more complex disease that is more difficult to treat with BPA.

The efficacy of BPA in our cohort was comparable to early reports from other European centers,[5–7,14] but results from the Japanese centers and later European experience generally show a better outcome. The patients from our cohort were older compared to other centers (70 vs. 61–65 years)[5,7,15,16] making patient selection a possible explanation.[17] Furthermore, differences in pathobiology between European and Asian CTEPH patients may explain the difference in BPA outcome.[18] The higher volume and more experience in Japanese and the larger European centers could also explain the better results[2,4,5,11,15,19] which would suggest that BPA should be centralized to ensure highest possible operator volume and experience.

The beneficial effects of BPA were evident in both the PEA and Non-PEA but study design and patient selection does not allow for comparison between groups. Our findings in the PEA group are, however, similar to reports from the Japanese center in Tokyo and the Polish centers[8,11] whereas the high-volume surgical center at Papworth recently reported a less favorable outcome of BPA for patients with prior PEA.[6] We know that longstanding CTEPH induces vasculopathy[17] which could limit the response to BPA in our cohort making comparison between cohorts challenging, but should encourage future efforts to shorten treatment delay.

The rate of mild and moderate complications is higher in our cohort than in some European and Japanese centers evaluated by per-procedure, but better than the early French BPA data with a complication rate of 46% per patient.[5] The higher rate of complications could be explained by a learning curve for the BPA procedure, as reported from the French center.[5] Another explanation could be a higher proportion of PEA patients in our BPA cohort and that PEA patients are more prone to complications.[11] The explanation for the higher rate of complications and impaired treatment response is unknown, but with more sub-occluded lesions, larger balloons needed and a trend towards more segments treated per patient in our PEA cohort it suggests that disease burden is higher, more complex and may be more resistant to treatment and more prone to complications than Non-PEA patients.

Long term mortality after BPA in Denmark is comparable to other BPA reports and to surgical outcome data after PEA.[12,20] Most deaths were not related to CTEPH and the patient population had several comorbidities that likely confound CTEPH associated mortality.

This analysis has several limitations. (1) The small cohort, nonpropensity matched single center retrospective analysis of the outcome after BPA has obvious limitations (2) The PEA and Non-PEA groups have different baseline and disease characteristics. Therefore, comparison between groups (PEA vs. Non-PEA) and with other cohorts should be done with caution. (3) There is no strict protocol for PAH targeted medical therapy which makes interpretation of the hemodynamic evaluation difficult. (4) No long-term follow-up. (5) Only hemodynamic follow-up in 45 of 59 patients (of which 10

of the missing where from our initial period of our BPA program) which could introduce selection bias. (6) Hemodynamics were evaluated before last BPA procedure in some patients ($n = 7$) which may underestimate the hemodynamic effects of BPA.

In conclusion, BPA improved hemodynamics, functional class and biomarkers of right heart failure in CTEPH patients not eligible for PEA and in patients with persistent pulmonary hypertension after PEA. Complications are common although most of them are mild or moderate and more frequent in PEA patients. Whether an acceptable risk-benefit is expected from BPA in inoperable patients with CTEPH and patients previously operated by PEA should be investigated in prospective controlled or propensity matched studies.

AUTHOR CONTRIBUTIONS

Asger Andersen and Jens Erik Nielsen-Kudsk: designed the study. Asger Andersen, Jacob Valentin Hansen, Simone Juel Dragsbaek, Mads Jønsson Andersen, Gratien Andersen, Søren Mellemjkaer, Lars Bo Ilkjær, and Jens Erik Nielsen-Kudsk: collected, analyzed and interpreted the data. Asger Andersen: wrote first draft of the paper. Jacob Valentin Hansen, Simone Juel Dragsbaek, Mads Jønsson Andersen, Gratien Andersen, Søren Mellemjkaer, Lars Bo Ilkjær, and Jens Erik Nielsen-Kudsk: did critical review and improvements of the paper.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the institution (Aarhus University Hospital) and performed in accordance with the Danish Data Protection Act and national law.

ORCID

Asger Andersen http://orcid.org/0000-0002-9102-3130

TWITTER

Asger Andersen @DocAsger

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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