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Sex-Specific Differences in Chronic Thromboembolic Pulmonary Hypertension Treated with Balloon Pulmonary Angioplasty

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Abstract: Background/Objectives: Several studies describe the sex-specific difference in cardiovascular diseases. However, there are still limited research reporting the difference between men and woman with chronic thromboembolic pulmonary hypertension (CTEPH) treated with ballon pulmonary angioplasty (BPA). The aim of the study was to evaluate sex–specific differences in patients with CTEPH treated with BPA. Methods: This retrospective study included CTEPH patients treated with BPA. Patients' hemodynamic and clinical parameters were assessed at baseline and 3 months after completion of BPA treatment. Results: The study included 94 patients (44 women, 46.8%). At baseline women had higher systolic pulmonary arterial pressure (sPAP) (76±18.5 vs. 85±17.6 mmHg; p=0.03), and pulmonary vascular resistance (8.21 [5.55-10.17] vs. 9.89 [6.31-14.06] Wood Units; p=0.03), compared to men. There were no differences in clinical characteristics between sexes. At follow-up, women had lower sPAP (49 [41-54] vs. 43 [37-49] mmHg; p=0.04) and pulmonary capillary wedge pressure (10 [9-14] vs. 9 [8-11] mmHg; p=0.03), but higher cardiac index (2.57±0.53 vs. 2.82±0.50 L/min/m2; p=0.03), as well as better Dyspnea Borg Scale outcomes, compared to men. Women had greater reduction of mean pulmonary artery pressure (-43% vs. -37%; p=0.049) than men. Conclusions: At baseline, women with CTEPH had worse hemodynamic parameters than men despite similar clinical symptoms. However, women hemodynamic status was better after BPA therapy. Hence, women seem better adapted to the disease at baseline and respond better to the BPA. Further data are needed to investigate whether the management of CTEPH a patients should be sex–differentiated.

Keywords: pulmonary hypertension; chronic thromboembolic pulmonary hypertension; ballon pulmonary angioplasty; sex-specific differences

1. Introduction

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Cardiovascular diseases (CVD) remain the leading cause of death among women and men worldwide [1]. In most clinical trials in cardiology, men dominate, and women are underrepresented. However, in the case of various forms of pulmonary hypertension (PH), the opposite is true: women predominate quantitatively among the participants in clinical trials [2–5]. This is due to the fact that women are more susceptible than men to several forms of PH [6,7].

Chronic thromboembolic pulmonary hypertension (CTEPH) is a condition defined by elevated pressure in pulmonary vascular bed caused by partial occlusion of the pulmonary arteries due to organized persistent thrombi, often accompanied by remodeling of patent resistive pulmonary arterioles [8]. Based on registry data, the prevalence of CTEPH is approximately 25.8-38.4 per million [9–11]. Balloon pulmonary angioplasty (BPA) is a minimally invasive procedure that has become an effective treatment option for CTEPH patients who are ineligible for pulmonary endarterectomy (PEA) or present with persistent PH after surgery [8,12–14].

Sex-specific differences in CTEPH have been studied, with some evidence suggesting that women may be at higher risk for developing CTEPH.[15]. Some studies suggest that there may be differences in the clinical presentation, risk factors, and outcomes of CTEPH treated by PEA between males and females [16]. However, there is limited research on the differences between women and men in CTEPH treated with BPA.

Therefore, the aim of this study was to evaluate sex–specific differences in patients with CTEPH who were treated with BPA procedures.

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2. Materials and Methods

2.1. Study Design and Settings

This retrospective study included patients consulted by the CTEPH-team in the Department of Pulmonary Circulation, Thromboembolic Diseases, and Cardiology between October 2011 and September 2020. Medical history and clinical data were obtained retrospectively from patients' medical records. As this was a retrospective study, patients were routinely diagnosed and treated, and no additional interventions were performed. A positive opinion from the Bioethics Committee was obtained (L.dz.OIL/KBL/27/2018).

Within routine patient management, the CTEPH-team provided multi-specialist consultations, established the CTEPH diagnosis based on invasive measurement of hemodynamic parameters during right heart catheterization (RHC) [17] and results of imaging studies and then referred patients to appropriate treatment methods: PEA, BPA, medical therapy, or combined therapy involving more than one of the mentioned methods according to current guidelines [8,18–20].

Data regarding patients' characteristics were evaluated including age, anthropometric data, comorbidities, anticoagulant and supporting treatment and reasons for rejection from PEA. Hemodynamic data was obtained during RHC performed according to the current guidelines [17]. In addition, functional class defined by World Health Organization was noted, and results of 6-minute walking test (6-MWT) and Borg dyspnea scale ratings after 6-MWT were collected. Laboratory tests were performed including the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) – reference value <125 pg/ml, high-sensitive troponin T – reference value <0.014 ng/ml and creatinine – reference value <0.9 mg/dl for women; <1.20 mg/dl for men.

Data of patients were analyzed at two points of time: at baseline and at follow-up. "Baseline" was defined as the moment of RHC performed before the first BPA procedure. "Follow-up" tests were performed, three to six months, after the last BPA procedure.

2.2. Statistical Analysis

Statistical analysis was performed with Statistica PL software (version 13, StatSoft, Tulsa, OK, USA). Categorical variables were presented as numbers and percentages. Continuous variables were presented as mean and standard deviation or median with interquartile range, depending on the distribution of the analyzed variable assessed using the Shapiro–Wilk test. The Chi-square test for categorized variables and Mann-Whitney U test for continuous variables were used to determine the differences between groups. For categorical variables with more than two categories, also Chi-square test was used. Statistical significance in the study was established at $p < 0.05$.

3. Results

3.1. Patients

From 417 consulted patients, 128 were included into the study (Figure 1). In 21 patients subsequent BPA sessions were planned; in 11 cases, due to the patient's mortality, the BPA series were unfinished, and follow-up was not performed. Contact loss occurred in 2 cases before the treatment with BPA was completed. Hence, the final population included 94 patients who terminated BPA treatment and had follow-up tests performed after the last BPA session. Among them, there were 44 (46.8%) females and 50 (53.2%) males.

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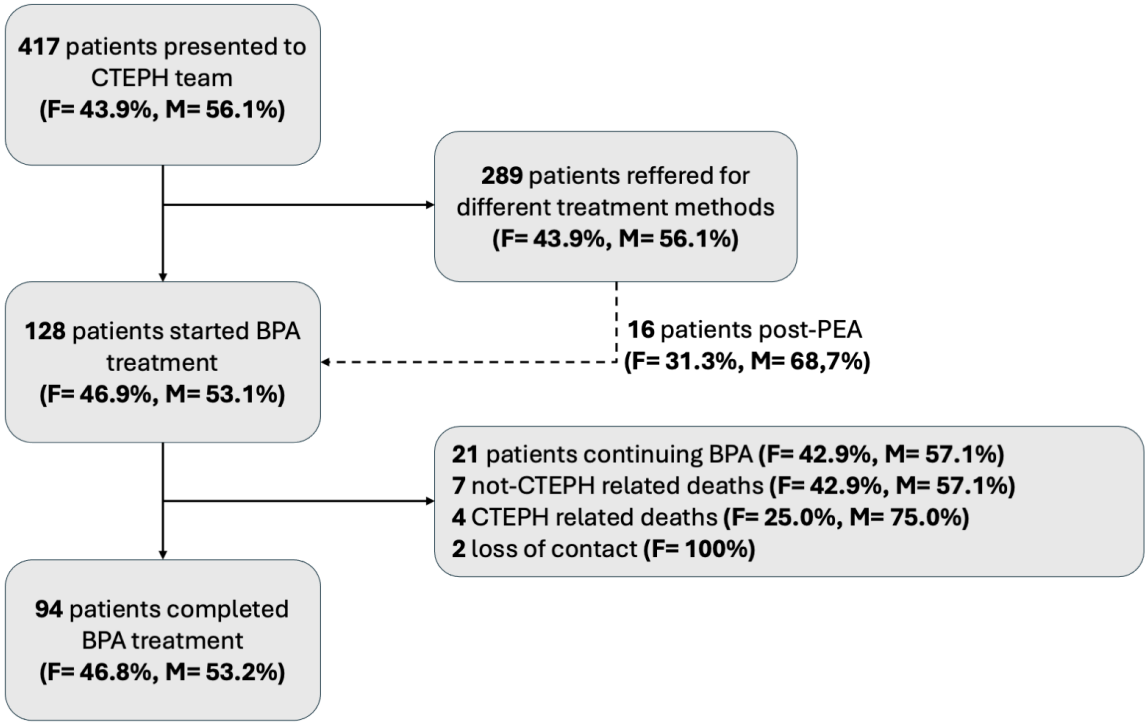

Figure 1. Flow chart of patient selection to the study. BPA – ballon pulmonary angioplasty; CTEPH – chronic thromboembolic pulmonary hypertension; F – female, M – male.

3.2. Evaluation at Baseline

Women were nominally younger than men (median 54 [47-70] vs. 66 [54-73] years) however the differences were not statistically significant (p=0.07). Men were significantly taller and heavier and had greater body surface area, but not BMI. Regarding comorbidities, men were more likely to suffer from chronic obstructive pulmonary disease (COPD). No differences were observed regarding the anticoagulant treatment used – over half of both women and men used DOAC, and no differences regarding the use of specific medical therapy. There were also no significant differences in the reasons for rejection from PEA – the most common reason was distal pulmonary vascular obstruction in both men and women (Table 1).

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Table 1. Characteristics of patients at baseline.

Variable		Female (n=44)	Male (n=50)	p-value
Age, years		54 [47-70]	66 [54-73]	0.07
Anthropometric measures	Weight, kg	67 [61-74]	81 [74-93]	<0.001
	Height, cm	162 (7.8)	175 (7.4)	<0.001
	BSA, m^2	1.73 (0.18)	1.98 (0.17)	<0.001
	BMI, kg/m^2	25.6 [23.3-28.4]	26.8 [24.5-29.9]	0.19
Comorbidities	Previous venous thrombosis, %	19 (43.2)	26 (52.0)	0.42
	Previous acute pulmonary embolism, %	37 (84.1)	36 (72.0)	0.22
	Hypertension, %	19 (43.2)	28 (56.0)	0.30
	Diabetes, %	2 (4.6)	7 (14.0)	0.23
	Coronary artery disease, %	9 (20.5)	14 (28.0)	0.47
	Hyperlipidemia, %	13 (29.6)	19 (38.0)	0.51
	Chronic obstructive pulmonary disease, %	0 (0.0)	13 (26.0)	<0.001
	Chronic kidney disease, %	8 (18.2)	10 (20.0)	1.00
	Atrial fibrillation, %	4 (9.1)	12 (24.0)	0.10
	Inferior vena cava filter, %	6 (13.6)	5 (10.0)	0.75
Anticoagulant treatment	VKA, %	12 (27.3)	14 (28.0)	0.75
	LMWH, %	7 (15.9)	9 (18.0)	
	DOAC, %	24 (54.6)	27 (54.0)	
PH specific therapy	Sildenafil or riociguat, %	36 (81.8)	39 (78.0)	0.71
	Oxygen therapy, %	8 (18.2)	7 (14.0)	0.58
Reasons for rejection from PEA	Distal pulmonary vascular obstruction, %	28 (63.6)	26 (52.0)	0.33
	Comorbidities, %	6 (13.6)	10 (20.0)	
	Lack of patient consent, %	5 (11.4)	3 (6.0)	
	Post-PEA CTEPH, %	5 (11.4)	11 (22.0)	

Data are presented as n (%), median [interquartile range] or mean (SD). BMI – body mass index; BSA – body surface area; DOAC – direct oral anticoagulants; PEA – pulmonary endarterectomy; PH – pulmonary hypertension; LMWH – low molecular weight heparin; SD – standard deviation; VKA – vitamin K antagonists

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Most of women and men presented the symptoms of III and IV WHO Functional Class at baseline. There was no difference between women and men regarding the severity of dyspnea assessed with the Borg scale after 6-MWT. Men presented higher serum levels of creatinine (Table 2).

Table 2. Patients' clinical status at baseline.

Variable		Female (n=44)	Male (n=50)	p-value
Heart rate, bpm		77 [66-92]	72 [65-78]	0.09
WHO FC, n (%)	1	0	0	0.69
	2	9 (20.5)	10 (20.0)	
	3	32 (72.7)	34 (68.0)	
	4	3 (6.8)	6 (12.0)	
6-MWT, m		341 (135.8)	366 (135.3)	0.43
Borg Dyspnea Scale, points (%)	0	17 (50.0)	22 (62.9)	0.89
	1	0	0	
	2	4 (11.8)	4 (11.4)	
	3	5 (14.7)	3 (8.6)	
	4	2 (5.9)	1 (2.9)	
	5	3 (8.8)	3 (8.6)	
	6	0	0	
	7	0	0	
	8	3 (8.8)	2 (5.7)	
	9	0	0	
	10	0	0	
Laboratory tests	NT-proBNP, pg/mL	1195 [412-1970]	1367 [652-2533]	0.71
	Troponin T, ng/mL	0.011 [0.006-0.021]	0.015 [0.009-0.026]	0.07
	Creatinine, mg/dL	0.86 [0.80-0.98]	1.13 [0.99-1.30]	<0.001

Data are presented as n (%), median [interquartile range] or mean (SD). 6-MWT – 6-minute walking test; NT-proBNP – N-terminal pro-B-type natriuretic peptide; SD – standard deviation; WHO FC – World Health Organization functional class

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Hemodynamic measurements at baseline (Table 3) showed that women had higher values of systolic pulmonary arterial pressure (sPAP) and pulmonary vascular resistance (PVR). In turn, men had higher stroke volume (SV).

Table 3. Patients' hemodynamic status at baseline.

Variable	Female (n=44)	Male (n=50)	p-value
mRAP, mmHg	7 [5-10]	9 [5-12]	0.31
sPAP, mmHg	85 (17.6)	76 (18.5)	0.03
dPAP, mmHg	29 (7.9)	28 (8.1)	0.56
mPAP, mmHg	49 (10.7)	45 (10.5)	0.08
PCWP, mmHg	9 [6-12]	10 [9-12]	0.30
CI, L/min/m^2	2.24 [1.81-2.80]	2.24 [1.92-2.50]	0.70
SV, mL/beat	54 (17.2)	64 (17.5)	0.01
SVI, mL/beat/m^2	31.59 (9.9)	31.91 (7.9)	0.86
PVR, Wood Units	9.89 [6.31-14.06]	8.21 [5.55-10.17]	0.03

Data are presented as median [interquartile range] or mean (SD). CI – cardiac index; dPAP – diastolic pulmonary arterial pressure; mPAP – mean pulmonary artery pressure; mRAP – mean right atrial pressure; PCWP – pulmonary capillary wedge pressure; PVR – pulmonary vascular resistance; SD – standard deviation; sPAP – systolic pulmonary arterial pressure; SV – stroke volume; SVI – stroke volume index

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3.2. Evaluation at Follow-Up

After BPA procedures, there were no differences in the number of sessions (median: 5; IQR: 4-7), the number of treated vessels during one session (mean: 7, SD 2.5) or the required amount of contrast (mean: 253 mL, SD 42.8), and radiation (median: 146 mGy; IQR: 90-248) between men and women. There were no differences in WHO functional classes of CTEPH regarding gender with most females and males presenting WHO class I or II after the BPA treatment was finished (Table 5). Serum levels of troponin and creatinine were significantly higher in men than in women. Evaluation with Dyspnea Borg scale after 6-MWT revealed some differences between sexes – 94.9% of women reported none or mild dyspnea while 20.4% of men reported moderate to rather/very intense dyspnea (Table 4).

Table 4. Patients' clinical outcomes at follow-up.

Variable		Female (n=44)	Male (n=50)	p-value
Heart rate, bpm		68 [61-78]	67 [59-78]	0.53
WHO FC, n (%)	1	14 (31.8)	13 (26.0)	0.59
	2	20 (45.5)	28 (56.0)	
	3	10 (22.7)	9 (18.0)	
	4	0	0	
6-MWT, m		428 (134)	444 (134)	0.57
6-MWT, Δm		+93 (96.6)	+76 (108)	0.47
Borg Dyspnea Scale, points (%)	0	34 (87.2)	35 (79.6)	0.03
	1	0	0	
	2	3 (7.7)	0	
	3	0	2 (4.5)	
	4	0	1 (2.6)	
	5	0	4 (10.5)	
	6	0	1 (2.6)	
	7	2 (5.1)	0	
	8	0	0	
	9	0	0	
	10	0	0	
Laboratory tests	NT-proBNP, pg/mL	152 [87-376]	223 [73-743]	0.60
	Troponin T, ng/L	0.007 [0.004-0.012]	0.014 [0.009-0.022]	<0.001
	Creatinin, mg/dL	0.79 [0.72-0.90]	1.05 [0.96-1.20]	<0.001

Data are presented as n (%), median [interquartile range] and mean (SD). 6-MWT – 6-minute walking test; NT-proBNP – N-terminal pro-B-type natriuretic peptide; WHO FC – World Health Organization functional class

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Post-treatment RHC data are presented in the Table 5. Men had higher sPAP compared to women, as well as pulmonary arterial wedge pressure. In turn, women had higher mean value of cardiac index.

Table 5. Patients' hemodynamic outcomes at follow-up and changes in some variables from baseline to follow-up.

Variable	Female (n=44)	Male (n=50)	p-value
mRAP, mmHg	5 [4-7]	6 [3-7]	0.77
sPAP, mmHg	43 [37-49]	49 [41-54]	0.04
dPAP, mmHg	15 [12-18]	17 [13-22]	0.05
mPAP, mmHg	26 [22-30]	29 [23-33]	0.11
Δnominal	-20.9 [±12.2]	-15.8 [±10.8]	0.04
Δ%	-43% [-57 – 25]	-37% [-47 – -18]	0.049
PCWP, mmHg	9 [8-11]	10 [9-14]	0.03
CI, L/min/m^2	2.82 (0.50)	2.57 (0.53)	0.03
Δnominal	+0.40 [±0.77]	+0.30 [±0.50]	0.42
Δ%	+16% [-1 – 51]	+11% [-5 – 32]	0.34
SV, mL/beat	70.87 (14.37)	76.62 (20.02)	0.12
SVI, mL/beat/m^2	40.77 (7.61)	38.33 (9.21)	0.17
PVR, Wood Units	3.34 [2.63-3.87]	3.08 [2.58-4.49]	0.65
Δnominal	-6.64 [-10.28 – -2.85]	-3.85 [-6.48 – -1.77]	0.048
Δ%	-62% [-79 – -42]	-54% [-69 – -36]	0.12

Data are presented as median [interquartile range] or mean (SD). CI – cardiac index; dPAP – diastolic pulmonary arterial pressure; mPAP – mean pulmonary artery pressure; mRAP – mean right atrial pressure; PCWP – pulmonary capillary wedge pressure; PVR – pulmonary vascular resistance; SD – standard deviation; sPAP – systolic pulmonary arterial pressure; SV – stroke volume; SVI – stroke volume index;

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3.3. Treatment Outcomes

Analyzing the results of the CTEPH treatment with BPA, the classification of patients according to WHO class improved. Proportions of both women and men being class I-II and III-IV reversed at follow-up when compared with baseline outcomes (Figure 2).

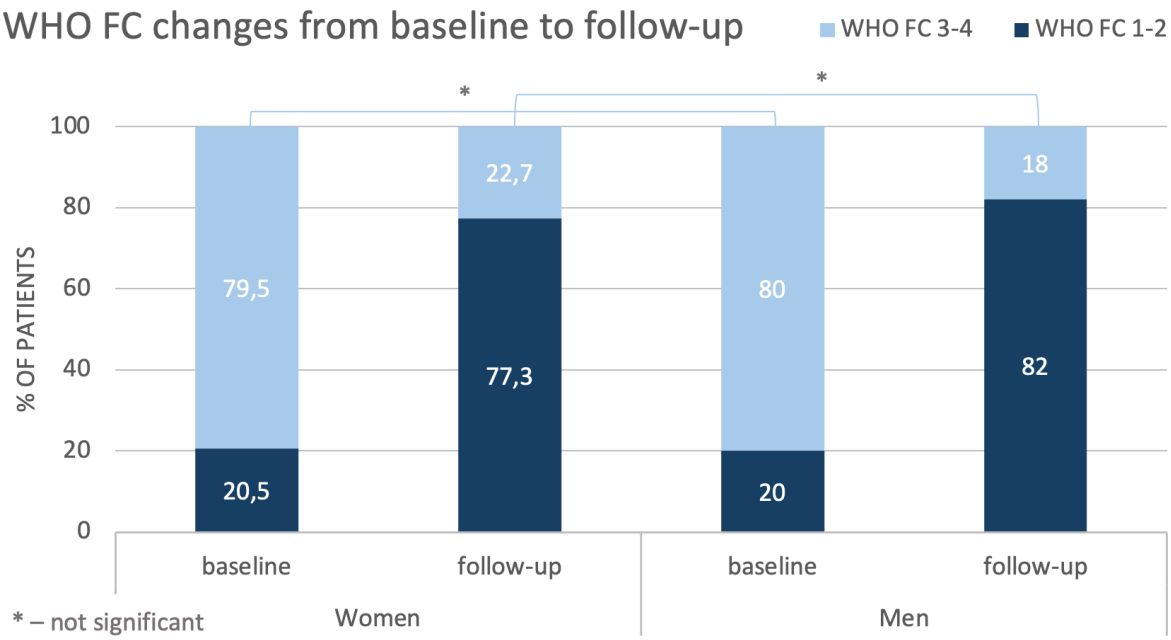

Figure 2. Comparison of changes in WHO FC in women and men from baseline to follow-up. WHO FC – World Health Organization functional class.

Also, outcomes of Borg Dyspnea Scale improved, but benefits were more pronounced for women than for men (Figure 3).

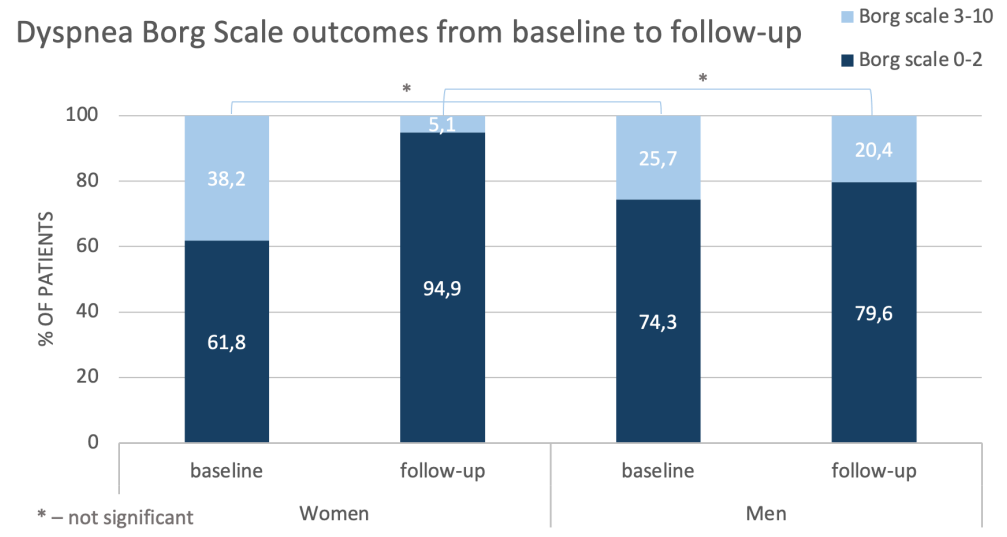

Figure 3. Comparison of changes in outcomes of Dyspnea Borg Scale in women and men from baseline to follow-up.

Additionally, detailed analysis of RHC results at baseline and at follow-up was performed. Percentage changes of hemodynamic variables are graphically presented at Figure 4.

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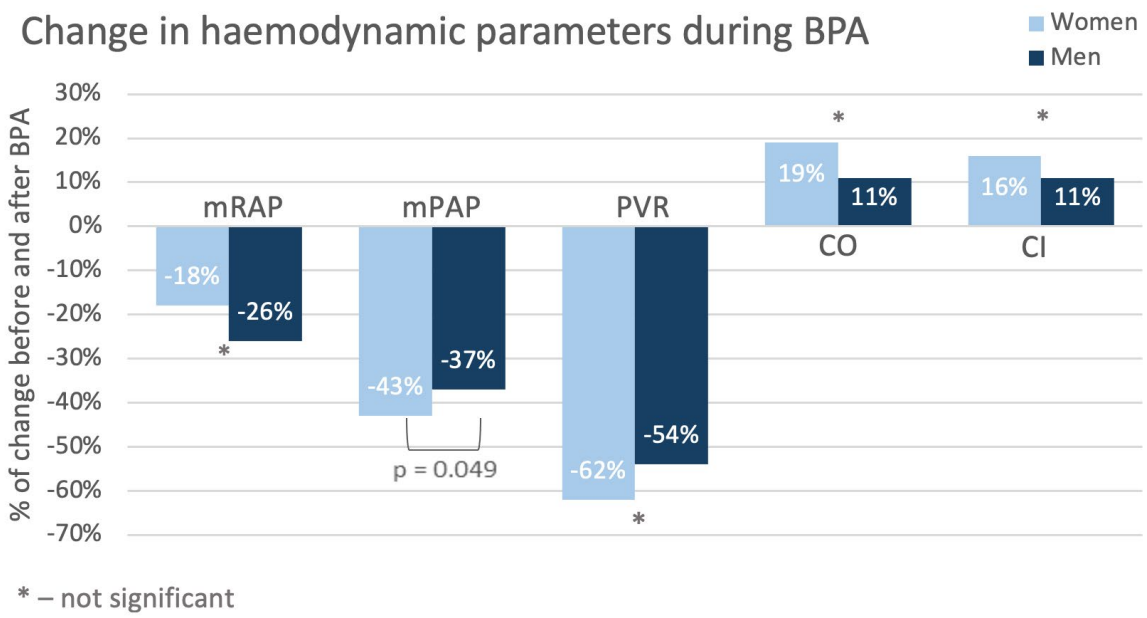

Figure 4. Changes in values of hemodynamic variable during treatment (from baseline to follow-up). CI – cardiac index; CO – cardiac output; mPAP – mean pulmonary artery pressure; mRAP – mean right atrial pressure; PVR – pulmonary vascular resistance.

The values (both nominal and percentage) of mean pulmonary arterial pressure (mPAP) in women decreased more than in men (-20.9 mmHg vs. -15.8 mmHg, p=0.04; -43% vs -37%, p=0.049). Also, pulmonary vascular resistance (PVR) in women was nominally lower, than in men. but this observation regarded only nominal values (-6.64 j.W. vs. -3.85 j.W. p=0.048; -62% vs. -54%, p=0.12) Detailed hemodynamics variables changes is presented in the Table 5.

Table 5. Patients' hemodynamic outcomes at follow-up and changes in some variables from baseline to follow-up.

Variable	Female (n=44)	Male (n=50)	p-value
mRAP, mmHg	5 [4-7]	6 [3-7]	0.77
sPAP, mmHg	43 [37-49]	49 [41-54]	0.04
dPAP, mmHg	15 [12-18]	17 [13-22]	0.05
mPAP, mmHg	26 [22-30]	29 [23-33]	0.11
Δnominal	-20.9 [±12.2]	-15.8 [±10.8]	0.04
Δ%	-43% [-57 – 25]	-37% [-47 – -18]	0.049
PCWP, mmHg	9 [8-11]	10 [9-14]	0.03
CI, L/min/m²	2.82 (0.50)	2.57 (0.53)	0.03
Δnominal	+0.40 [±0.77]	+0.30 [±0.50]	0.42
Δ%	+16% [-1 – 51]	+11% [-5 – 32]	0.34
SV, mL/beat	70.87 (14.37)	76.62 (20.02)	0.12
SVI, mL/beat/m²	40.77 (7.61)	38.33 (9.21)	0.17
PVR, Wood Units	3.34 [2.63-3.87]	3.08 [2.58-4.49]	0.65

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Δnominal	-6.64 [-10.28 – -2.85]	-3.85 [-6.48 – -1.77]	0.048
Δ%	-62% [-79 – -42]	-54% [-69 – -36]	0.12

Data are presented as median [interquartile range] or mean (SD). CI – cardiac index; dPAP – diastolic pulmonary arterial pressure; mPAP – mean pulmonary artery pressure; mRAP – mean right atrial pressure; PCWP – pulmonary capillary wedge pressure; PVR – pulmonary vascular resistance; SD – standard deviation; sPAP – systolic pulmonary arterial pressure; SV – stroke volume; SVI – stroke volume index

4. Discussion

CTEPH is a rare condition, but it can lead to right heart failure, multiorgan disfunction, and death if left untreated. The BPA therapy which has been used relatively recently in the treatment of patients with CTEPH [21,22], has been upgraded in the recent guidelines for CTEPH treatment, which currently recommended BPA as a part of multimodal approach for patients who have inoperable lesions or have residual PH after PEA and distal obstructions amenable to BPA (class of recommendation IB). This procedure may also be applied to those patients who are operable but have a high proportion of distal disease and a PEA procedure may generate a high risk for them. BPA can also be considered in some symptomatic patients with CTEPD without PH [8].

The recent study which analyzed preoperative computed tomography pulmonary angiography of patients who underwent PEA for CTEPH identified sex-specific differences in the surgical cases [23]. Men had more vessels involved than women (mean 20.3 vs 17.1, $p = 0.004$) and had fewer disease-free pulmonary segments (mean 4.9, SD 4.3 vs 7.6, SD 5.5, $p = 0.001$). In addition, men had a greater number of webs, eccentric thickening, and occlusions. The distribution of lesion type did not significantly differ between sexes at the main or lobar level, but men had significantly more lesions in the segmental vasculature while women had a higher proportion of subsegmental lesions ($p < 0.001$) despite no significant differences in baseline hemodynamics [23]. Although, it was described that after PEA women benefit less in reduction of PVR (437 Dynes·s·cm−5 vs 324 Dynes·s·cm−5 in males, $p < 0.01$), the overall 10-years survival after surgical treatment was similar (73% in females vs 84% in males, $p = 0.08$) [24]. In multivariate analysis female sex remained an independent factor affecting the need for targeted PH medical therapy after PEA (HR 2.03, 95%CI 1.03–3.98, $p = 0.04$), which suggests other mechanisms may be responsible for worse response to surgical treatment in females with proximal disease [24].

There is a lack of data, whether sex affects BPA results. Therefore, we aimed at evaluation whether differences exist between men and women with CTEPH and to evaluate if outcomes of treatment with BPA differs regarding sex/gender. Women are known to be more susceptible to PH than men, and therefore usually among patients with CTEPH, but on the other hand women have also better survival [16,25,26]. In the case of CTEPH, the latest publication based on European registry indicated an equal ratio of affected women and men [16], similarly as US registry [27]. Registry developed by International CTEPH Association reported general dominance of women (52.4%), however in Europe they made up slightly less than half (48.7%) of patients with CTEPH [28]. (Figure 5 [14,19,27–34]).

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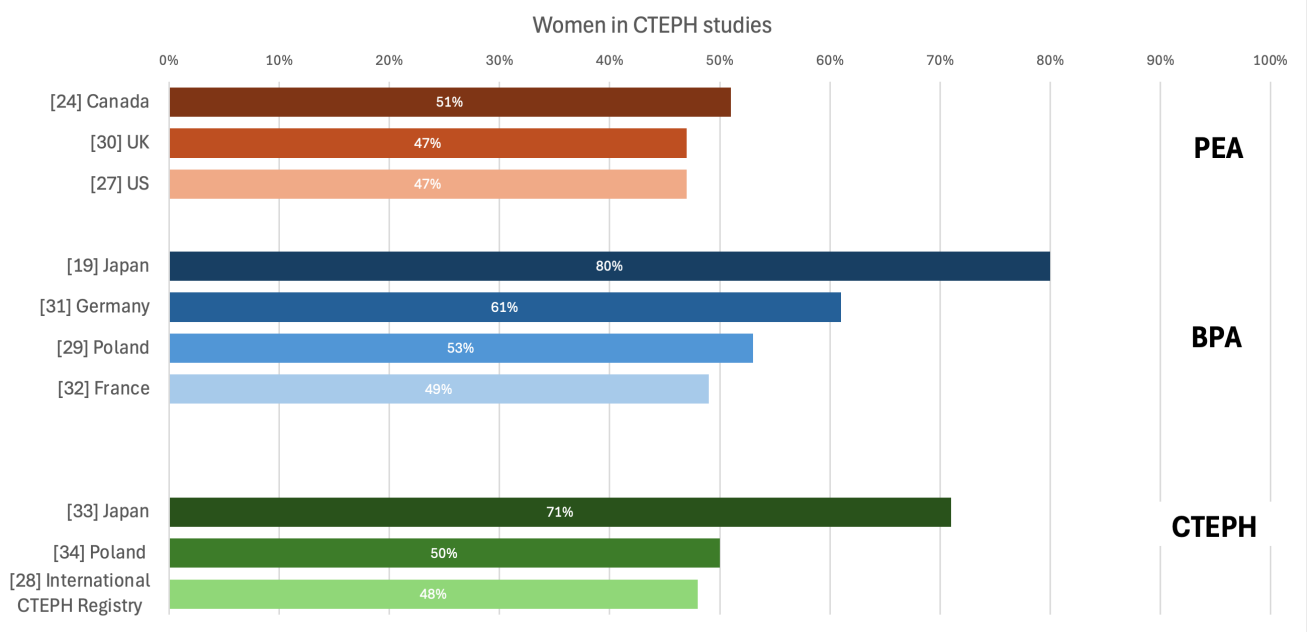

Figure 5. Percentage of women represented in CTEPH studies [14,19,27–34]. BPA – ballon pulmonary angioplasty; CTEPH – chronic thromboembolic pulmonary hypertension; PEA – pulmonary endarterectomy.

European registry indicated that women had lower prevalence of some CV risk factors than men, such as previous acute coronary syndrome, smoking and COPD, but more often were obese, and had cancer or thyroid diseases history [16]. Women and men included in our study did not differ in terms of comorbidities, except for the occurrence of COPD that was much less frequently diagnosed in women.

As the CTEPH is strongly associated with the occurrence of pulmonary embolism and an incomplete thrombus resolution [35], sex/gender differences related to coagulation should be also considered. Typical thrombogenic factors were not proved to increase in patients with CTEPH in contrast to plasma factor VIII [36,37]. This factor physiologically has higher values in women than in men [38], what may predispose women to developing CTEPH. In the Japanese BPA Registry females represented 80% of included patients, and previous episodes of acute pulmonary embolism and deep vein thrombosis were not frequent (15,3% and 43,7% respectively) [19], as compared with reports from other Western countries (74.8% and 58.1%, respectively, in a European registry) [39].

Assessing patients' status at baseline, we found that woman tended to have worse hemodynamics values than men, as indicated by higher sPAP and PVR and by lower SV. Creatinine levels were slightly higher in men, but this may probably result from physiologically higher muscle mass in men. In turn, clinical presentation in women and men was quite similar – there were no significant differences between sex/gender in results of Dyspnea Borg Scale and also in the distance walked during 6-MWT. Our population also did not differ in terms of WHO FC and most patients were diagnosed with WHO FC class 3. This observation is consistent with results described in other studies [26,28,40] and also with observations from European CTEPH registry [16], indicating that women slightly more often have functional capacity class III/IV diagnosed than men. More severe courses of the disease in women than men with CTEPH was also reported by Wu et al [41].

More severe baseline hemodynamic parameters in women compared with men together with similar clinical symptomatology suggest that at diagnosis women are better adapted to the disease than men. On the other hand, it may be hypothesized that women will require more BPA sessions to achieve similar improvements in hemodynamics as men.

As there are no detailly defined therapeutic targets of BPA treatment in patients with CTEPH, usually achieving a good functional class (WHO-FC I–II) and/or improvement of hemodynamic parameters, as well as improvement in patients' quality of life [8]. However, some recent data from ESC Working Group Statement defined BPA treatment goal to achieve final mPAP < 30 mmHg [42].

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Comparing the effects of BPA from two multicenter registries (Japanese and Polish) and from single expert-centers (German and French) it was demonstrated that only Japanese were able to reach defined BPA treatment goal of mPAP below 30 mmHg [43]. This may be due to the intrinsic differences between European and Japanese patients, with European CTEPH patients having higher serum concentrations of C-reactive protein, fibrinogen and myeloperoxidase, and more red thrombus than Japanese CTEPH patients [44]. However, high-volume women representation in Japanese registry may be also suggestive for gender-related outcome in BPA treatment.

Control tests performed in the studied population after completion of BPA treatment revealed better hemodynamic status (especially regarding mSAP, sPAP, PCWP and CI) in women than in men, although at baseline the situation was opposite. Detailed analysis demonstrated that after treatment many parameters changed more in women than in men with decreases in mPAP and PVR being the most pronounced. These were reflected particularly in outcomes of Dyspnea Borg Scale – compared with baseline at follow-up in about 30% of women ratings shifted towards point 0-2 and such improvement was observed only by about 5% of men. Results of 6-MWT this difference did not achieve statistical significance.

Our results are even more interesting considering that there were no differences in number of the sessions, number of the treated vessels or the required amount of contrast and radiation between men and women. This may suggest that women respond better to CTEPH treatment with BPA than men.

The above observation seems to stay in line with the previously reported better long-term survival in women compared with men. This phenomenon is suggested to be related to better function of right ventricular in females than in males [45,46]. Unfortunately, echocardiographic data were unavailable in our study, hence we were unable to assess right ventricular functions in our population. However, that hemodynamic differences exist between different types of CTEPH with a worse condition in central than in peripheral form of disease [47]. Besides, in some studies, women tended to deteriorate more than males during follow-up [48].

Strengths and Limitations of the Study

To our knowledge this is the first very detailed study analyzing the impact of patients' sex/gender on results of BPA therapy in patients with CTEPH. As it was a retrospective (single center, small group) study, we were able to provide valuable data from real clinical practice. However, some assessments are missing which is an inherent limitation to this type of research.

5. Conclusions

Although many studies demonstrated that BPA improves both hemodynamic parameters and clinical status of patients with CTEPH [49,50], sex/gender-specific treatment results are unknown. Also, current guidelines do not promote any sex/gender-specific approach, which implies that the diagnostic-therapeutic process is the same in women and men. Therefore, our data may be used to initiate further studies analyzing different scenarios of clinical management depending on sex/gender. We observed that at diagnosis women had more severe hemodynamic parameters than men that were accompanied by similar clinical symptomatology in both sexes. Despite this, women hemodynamic status was better after BPA therapy. The above outcomes may suggest that at diagnosis women are better adapted to the disease than men, and also women respond better to the BPA treatment. However, we are aware that these data are just preliminary and research evidence from the randomized controlled trials is needed to demonstrate whether the management of a patient with CTEPH should be sex – differentiated.

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Abbreviations

The following abbreviations are used in this manuscript:

BPA	Ballon pulmonary angioplasty
CTEPH	Chronic thrombo-embolic pulmonary hypertension
CVD	Cardiovascular diseases
RHC	Right heart catherization
PEA	pulmonary endarterectomy
6-MWT	6-minute walking test
NT-proBNP	N-terminal pro-B-type natriuretic peptide
M	Male
F	Female
BMI	Body mass index
DOAC	Direct oral anticoagulants
PH	Pulmonary hypertension
SD	Standard deviation
VKA	Vitamin K antagonists
LMWH	Low molecular weight heparin
WHO FC	World Health Organization functional class
mRAP	mean right atrial pressure
sPAP	systolic pulmonary arterial pressure
dPAP	diastolic pulmonary arterial pressure
mPAP	mean pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
CI	cardiac index
SV	stroke volume
SVI	stroke volume index
PVR	pulmonary vascular resistance
IQR	Interquartile range
COPD	Chronic obstructive pulmonary disease

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