MARMARA
MEDICAL JOURNAL

Original Article

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# The impact of right ventricular energy failure on the results of pulmonary endarterectomy and balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension

Redwan Seid BUSERY[1], Bulent MUTLU[1], Dursun AKASLAN[2], Emre ASLANGER[3], Bedrettin YILDIZELI[4], Halil ATAS[1]

[1] Department of Cardiology, School of Medicine, Marmara University, Pendik Training and Research Hospital, Istanbul, Turkey
[2] Cardiology Clinic, Antalya City Hospital, Antalya, Turkey
[3] Cardiology Clinic, Başakşehir Pine and Sakura City Hospital, Istanbul, Turkey
[4] Thoracic Surgery, School of Medicine, Marmara University, Pendik Training and Research Hospital, Istanbul, Turkey

**Corresponding Author:** Redwan Seid BUSERY
**E-mail:** redwan.900@gmail.com

**Submitted:** 25.03.2024 **Accepted:** 07.05.2024

ABSTRACT

Objective: We aimed to investigate the effect of right ventricular energy failure (RVEF) on hemodynamic and clinical outcomes in patients diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) undergoing pulmonary endarterectomy (PEA) surgery or balloon pulmonary angioplasty (BPA).

Patients and Methods: A total of 100 CTEPH patients planned for PEA or BPA were included in the study. Based on the presence of RVEF during diagnosis, patients divided into two groups. Hemodynamic data from right heart catheterization (RHC) were compared before and after procedures in 3-6 months follow up period.

Results: Patients with RVEF revealed a decrease in mean pulmonary artery pressure (mPAP) from 54.67±12.27 mmHg to 36.12±11.76 mmHg (p:<0.001), mean right atrial pressure (mRAP) from 13.40±4.08 mmHg to 9.76±4.56 mmHg (p:0.003), and pulmonary vascular resistance (PVR) from 11.36±5.15 Wood Units (WU) to 5.46±3.30 WU (p <0.001). In the non-RVEF group, mPAP decreased from 38.82±12.61 mmHg to 30.81±10.57 mmHg (p:<0.001), mRAP from 7.09±3.02mmHg to 7.15±3.07mmHg (p: 0.917), and PVR from 6.33±3.65 WU to 4.09±2.31 WU (p:<0.001).

Conclusion:The presence of RVEF at the time of diagnosis in CTEPH patients does not have a negative impact on early perioperative and 3-month postoperative outcomes following PEA or BPA. This high-risk patient group demonstrated significant hemodynamic and clinical benefits from both PEA and BPA.

Keywords: Chronic thromboembolic pulmonary hypertension, Right ventricular energy failure, Pulmonary endarterectomy, Pulmonary balloon angioplasty

## 1. INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and progressive disease that occurs as a result of the occlusion of the pulmonary arteries by organized blood clots. The diagnosis of CTEPH is established by the presence of filling defects in two or more segments on ventilation-perfusion scintigraphy (V/Q), visualization of obstructive or flow-limiting material in the pulmonary arteries using computed tomography pulmonary angiography (CTPA) and/or selective pulmonary angiography with digital subtraction angiography (DSA). A diagnosis of CTEPH is made when, after at least 3 months of effective anticoagulation therapy for pulmonary embolism (PE) diagnosis, the mean pulmonary artery pressure (mPAP) is greater than 20 mmHg on the right heart catheterization (RHC), the pulmonary capillary wedge pressure (PCWP) is less than 15 mmHg, and the pulmonary vascular resistance (PVR) is greater than 2 Wood Units (WU). If imaging methods demonstrate the disease but pulmonary hypertension is not detected on RHC, a diagnosis of chronic thromboembolic pulmonary disease (CTEPD) is made [1].

The treatment algorithm for CTEPH includes a multimodal approach consisting of pulmonary endarterectomy (PEA) targeting anatomical lesions, balloon pulmonary angioplasty (BPA), and combinations of medical therapies. PEA is the

**How to cite this article:** Busery SR, Mutlu B, Akaslan D, Aslanger E, Yildizeli B, Atas H. The impact of right ventricular energy failure on the results of pulmonary endarterectomy and balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. Marmara Med J 2024: 37(2):129-136. doi: 10.5472/marumj.1484403


ISSN: 1309-9469



http://doi.org/10.5472/marumj.1484403
**Marmara Med J 2024;37(2): 129-136**

preferred and gold standard treatment method significantly improving pulmonary hemodynamics and functional capacity in CTEPH patients with accessible lesions [2].

Balloon pulmonary angioplasty has become a treatment option that improves right heart function and exercise capacity in patients who are not suitable for PEA surgery due to technical reasons or comorbidities, or in those who develop pulmonary hypertension after PEA due to residue CTEPH [3,4].

In pulmonary hypertension and CTEPH patients, an increased PVR in the pulmonary vascular bed leads to workload on the right ventricle, eventually resulting in right heart failure. Clinical manifestations and mortality in patients are primarily driven by the development of right heart failure, which has prognostic implications. Right ventricular energy failure (RVEF) is defined by a ratio of left atrial (or PCWP) pressure to right atrial pressure <1, which provides more specific information about the patient's RV systolic performance related to their own pulmonary vascular status, independent of volume status, PVR, and RV systolic dysfunction levels [5-7].

In previous studies RVEF was defined as the RA pressure to PCWP ratio and has been investigated as predictor of long term mortality and 1 year survival rate in group 1 PH patients [7]. RVEF in CTEPH patients is similarly used in our study and to our knowledge there is no prospectively studied data on hemodynamic outcome after PEA and BPA procedure. The aim of this study is to investigate the impact of presence of right ventricular energy failure, at the time of diagnosis on the outcomes of PEA surgery and BPA.

## 2. PATIENTS and METHODS

### *Study design*

This study was conducted at Marmara University, Pendik Training and Research Hospital, a tertiary center for pulmonary hypertension (PH) by the Department of Cardiology. Ethical approval for the study was obtained from the Clinical Research Ethics Board (18.04.2023 approval number: 09.2023.309), and the study was conducted in accordance with the Helsinki Declaration. Patients referred to our center with a diagnosis of CTEPH between February 2023, and October 2023 with a plan for PEA surgery or BPA intervention were included in the study. Post procedural findings were collected prospectively.

All patients were evaluated by a multidisciplinary team, including an experienced cardiothoracic surgeon specialized in PEA, an interventional cardiologist specialized in BPA, a pulmonologist, a rheumatologist, and a radiologist experienced in pulmonary hypertension. A comprehensive examination included transthoracic echocardiography, multislice computed tomographic angiography, ventilation/perfusion scintigraphy, right heart catheterization, and selective pulmonary angiography when necessary. All patients were evaluated for the diagnosis and management of CTEPH according the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for PH [1,8].

### *Inclusion and exclusion criteria*

Patients aged 18 and above, diagnosed with CTEPH, and deemed suitable for surgical or BPA procedures who consented to participate were included in the study. Pulmonary endarterectomy and BPA procedures were conducted at Marmara University Pendik Training and Research Hospital. Patients diagnosed with CTEPH but having significant valve disease (except functional tricuspid regurgitation), left ventricular systolic dysfunction (EF < 50%), and those with a prior diagnosis of atrial fibrillation were excluded from the study.

### *Study protocol*

### *Clinical and hemodynamic assessment*

In this cohort study, initial baseline assessment with detailed medical history, comorbidities and past treatment modalities, namely anticoagulant use and pulmonary vasodilator drug classes were documented. Follow-up findings were evaluated prospectively at 3 to 6 months after the completion of the appropriate treatment strategy.

Demographic findings were recorded in a previously prepared case follow-up forms. Blood samples were collected from all patients for complete blood count, renal function tests, liver function tests, and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. A 6-minute walk distance test (6MWT) was conducted by an experienced nurse, and all information was added to the case follow-up form.

Patients who underwent PEA or BPA received pre-procedural hemodynamic assessment via right heart catheterization (RHC) conducted by an interventional cardiologist specialized in this field. A 7-F Swan-Ganz catheter (Edwards Lifesciences) was inserted through femoral or jugular venous approach for RHC. Measurements included mean right atrial pressure (mRAP), right ventricular (RV) pressure, systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), mean pulmonary artery wedge pressure (mPAWP),

Patient's height, weight, and hemoglobin levels were noted, and using pulmonary artery and systemic saturations, cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) measurements were calculated via the Fick method. RVEF assessment utilized mRAP and PCWP. Right ventricular energy failure was defined as a ratio of mean PCWP to mean RA pressure ≤1.

All pressure tracings were visually inspected for physiological accuracy, and expiratory end pressure values were recorded. RHC reports were generated using a database program that records the findings of pulmonary hypertension patients within our institution and all parameters were reassessed during diagnosis and repeated 3-6 months after treatment.

### *Right ventricular energy failure (RVEF)*

Right ventricular energy failure (RVEF) is a condition where the heart's right ventricle cannot effectively pump blood, leading


http://doi.org/10.5472/marumj.1484403
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to various cardiac and pulmonary issues. This condition often results from increased pulmonary vascular resistance causing high pressure in the right ventricle, leading to right ventricular failure.

Right ventricular energy failure is typically evaluated by measuring parameters from right heart catheter findings mainly mean pulmonary artery pressure (mPAP) and mean right atrial pressure (mRAP). A defining feature of RVEF is the ratio of mPCWP to mRAP, and a ratio ≤1 indicates energy failure [7,9].

Utilizing RHC findings for patients diagnosed with CTEPH, the mPCWP and mRAP ratio were calculated for all patients, and based on the obtained value, patients were categorized into two groups: those with RVEF and those with no RVEF. The pre – and post-treatment RHC, 6MWT, NT-proBNP, and functional capacities of both groups were compared.

### Statistical Analysis

The data were analysed using IBM SPSS statistics (version 26.0; SPSS Inc., Chicago, Illinois). The distribution of variables was evaluated according to the Kolmogorov-Smirnov criteria. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were expressed as numbers and percentages.

Depending on the presence of subgroups of RVEF, the chi-square test, Student's t-test, and Mann-Whitney U test were used for comparisons of baseline parameters before and after the appropriate treatment accordingly. Two-way correlation analysis was performed using the Pearson test for normally distributed data and the Spearman test for non-normally distributed data. Statistical analyses with a p-value below 0.05 were considered significant.

## 3. RESULTS

### *Demographic data*

A total of 128 CTEPH patients were included in the study. 67 patients were evaluated as suitable for PEA through a multidisciplinary approach, and PEA was planned. Simultaneous coronary artery bypass graft surgery was performed in 3 of these patients. 3 patients declined PEA. Eight patients died, with 1 during PEA surgical preparation and 7 during the intensive care follow-up after the surgical procedure. A total of 12 patients could not undergo surgery due to technical reasons or unfavorable risk/benefit ratios. Among them, 4 had previously undergone PEA and were being followed for residual CTEPH. These patients were re-evaluated in the CTEPH council, and 2 were treated with BPA. The remaining 2 patients with residual CTEPH and the remaining 8 patients were followed with medical treatment only.

After selective pulmonary angiography and a comprehensive evaluation, BPA was decided as a treatment option for 43 patients. A total of 218 BPA sessions were performed on these patients and RHC and clinical evaluations were performed 3-6 months after the last BPA session. Of these, 100 patients were included in the final analysis of our study, 27 (27%) had RVEF, and 73 (73%) did not. The mean age of patients with RVEF was 47.96 ± 15.12 years, while the non-RVEF group had a mean age of 56.14 ± 13.97 years. In the RVEF group, 13 (48.1%) were male, while the non-RVEF group consisted of 35 (47.9%) males.

The NT-ProBNP values were 2297.48 ± 2881.93 ng/L and 1436.59 ± 1737.21 ng/L, respectively, for the RVEF and non-RVEF groups, and the 6MWT distances were 297.11 ± 122.35 m and 281.2 ± 114.0 m, respectively.

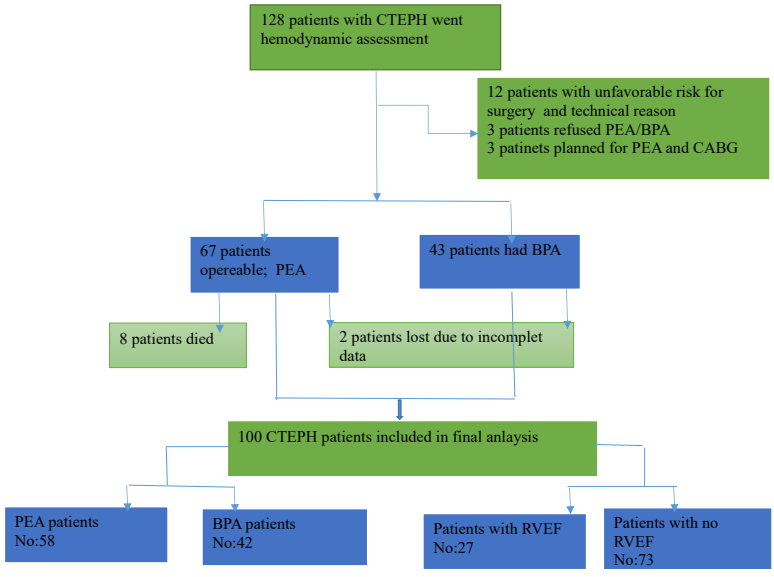


***Figure 1.*** *Patient selection and disposition*
*BPA: Balloon Pulmonary Angioplasty; CABG: Coronary Artery Bypass Graft; CTEPH: Chronic Thromboembolic Pulmonary Hypertension; PEA: Pulmonary Endarterectomy; RVEF: Right Ventricular Energy Failure*


http://doi.org/10.5472/marumj.1484403
Marmara Med J 2024;37(2): 129-136

In the RVEF group, 8 (29.6%) patients had controlled hypertension (HT), and 3 (11.1%) had controlled diabetes mellitus (DM). In the non-RVEF group, there were 42 (57.5%) with HT and 12 (16.4%) with DM. A history of coronary artery disease was found at 2 (7.4%) in the RVEF group and 7 (9.6%) in the non-RVEF group. All patients were on anticoagulant therapy. Of these, 42% were on warfarin, 33% on rivaroxaban, 20% on enoxaparin, and the remaining 5% were on other direct oral anticoagulant treatment (Table I).

***Table I.*** *Hemodynamic findings according to patients' demographic characteristics and the presence of RVEF.*

| Variables | RVEF present (27) | RVEF absent (73) | P value |
|---|---|---|---|
| **Demographic data** | | | |
| Age, years | 47.96 ±15.12 | 56.14±13.97 | 0.013 |
| Gender, male n(%) | 13(48.1%) | 35(47.9%) | 0.096 |
| BMI, kg./m2 | 25.57±7.37 | 28.15±5.32 | 0.056 |
| Hb, g/dl | 12.96±2.37 | 13.23±1.65 | 0.534 |
| NT-Probnp, ng/L * | 2052.50 (393.75 – 6017.85) | 1005.0 8(886.40 – 2082.14) | 0.072 |
| Creatinin, mg/dl | 0.84±032 | 0.81±0.23 | 0.666 |
| 6MWT, m | 297.11±122.35 | 281.2±114.0 | 0.547 |
| **Coomorbidities** | | | |
| HT | 8 (29.6%) | 42(57.5%) | 0.023 |
| DM | 3 (11.1%) | 12(16.4%) | 0.753 |
| Thyroid disorder | 5(18.5%) | 17(23.3%) | 0.787 |
| CAD | 2(7.4%) | 7(9.6%) | 1.000 |
| COPD | 5(18.5%) | 8(11%) | 0.329 |
| DVT | 10(37%) | 21( 28%) | 0.470 |
| **Hemodynamic parameters** | | | |
| PA systolic, mmhg | 91.38±20.36 | 65.32±22.15 | **<0.001** |
| PA diastolic, mmhg | 32.54±10.64 | 23.88±8.93 | **<0.001** |
| PA mean, mmhg | 54.92±11.80 | 38.77±12.75 | **<0.001** |
| Ao BP mean,mmhg | 93.37±17.14 | 95.71±18.90 | 0.558 |
| RA mean, mmhg | 13.37±3.93 | 7.15±2.99 | **<0.001** |
| CI, L/min/m2 | 2.28±0.54 | 2.63±0.63 | **0.010** |
| PVR, woods | 11.48±5.15 | 6.13±3.44 | **<0.001** |
| SaPO2 (%) | 93.27±3.80 | 93.53±4.05 | 0.778 |
| Pa O2 (%) | 58.82±10.81 | 65.25±6.92 | 0.001 |

*Values are mean ± standard deviation or number (percentage), unless specified otherwise.*
** median (interquartile range, IQR)*
*6MWT: six-minute walk test distances; Ao: Aortic; BMI: Body Mass Index; BNP: B-type Natriuretic Peptide; BP: Blood Pressure; CI: Cardiac Index; DM: Diabetes Mellitus; DVT: Deep Vein Thrombosis; Hb: Hemoglobin; HT: Hypertension; COPD: Chronic Obstructive Pulmonary Disease; mPAP: Mean Pulmonary Artery Pressure; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; PA: Pulmonary Artery; PAWP: Pulmonary Artery Wedge Pressure; PVR: Pulmonary Vascular Resistance; PaO2: Arterial Oxygen Partial Pressure; RA: Right Atrium; RV: Right Ventricle; SaO2: Arterial Oxygen Saturation; sPAP: Systolic Pulmonary Artery Pressure; SVR: Systemic Vascular Resistance.*

### *RHC Hemodynamic findings*

When looking at the RHC data obtained from patients with and without RVEF, the mean pulmonary artery pressure (mPAP) of patients with RVEF was 54.92 ± 11.80 mmHg, mean right atrial pressure (mRAP) was 13.37 ± 3.93 mmHg, pulmonary capillary wedge pressure (PAWP) was 9.96 ± 2.60 mmHg, and pulmonary vascular resistance (PVR) was 11.48 ± 5.15 WU.

For patients without RVEF, mPAP was 38.77 ± 12.75 mmHg, mRAP was 7.15 ± 2.99 mmHg, and PVR was 19.66 ± 6.20 WU.

Hemodynamic and clinical response to PEA surgery and BPA procedure according to presence of RVEF is shown in Table II. Patients with RVEF showed an increase in 6MWT after the procedure from 297.77 ± 124.72m to 370.12 ± 109.66m ($p < 0.001$ ) and a decrease in NT-proBNP values from 2280 ± 2937.63 , ng/L to 824 ± 941, ng/L ($p = 0.016$).

When examining the hemodynamic data of patients with RVEF, a statistically significant decrease was observed in mPAP from 54.67 ± 12.27mmHg to 36.12 ± 11.76mmHg, mRAP from 13.40 ± 4.08mmHg to 9.76 ± 4.56mmHg, PVR from 11.36 ± 5.15 WU to 5.46 ± 3.30 WU.

In patients without RVEF, a decrease in NT-proBNP values (from 1384.32 ± 1760.29 to 501.97 ± 722.16) and an increase in the 6MWT from 300.92 ± 104.96m to 348.63 ± 97.91m were observed after the procedure. This difference was found to be statistically significant for both parameters ($p < 0.001$) (Table II).


http://doi.org/10.5472/marumj.1484403
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***Table II.*** *Response to PEA surgery and BPA procedure in patients with RVEF and without RVEF.*

| Variables | Patients with RVEF | | | Patients without RVEF | | |
|---|---|---|---|---|---|---|
| | Pre procedure | Post procedure (PEA/ BPA) | P values | Pre procedure | Post procedure (PEA/BPA) | P values |
| Hb, g/dl | 12.85±2.33 | 12.82±2.05 | 0.923 | 13.25 ±1.63 | 13.65±1.44 | 0.101 |
| NT-Pro Bnp, ng/L * | 908.5 (361.3 – 3326.2) | 377.5 (131.2 – 1610.48) | **0.016** | 510.0 (290.8 – 2790.8) | 296.0 (95.5 8 – 1223.71) | **<0.001** |
| 6MWT, m | 297.77 ±124.72 | 370.12 ±109.66 | **<0.001** | 300.92±104.96 | 348.63±97.91 | **<0.001** |
| PA systolic, mmhg | 91.17±21.18 | 62.75±20.27 | **<0.001** | 66.03±22.42 | 51.57±18.573 | **<0.001** |
| PA diastolic, mmhg | 31.83±10.76 | 21.83±7.29 | **0.002** | 23.85±9.31 | 19.34±7.25 | **<0.001** |
| PA mean, mmhg | 54.67±12.27 | 36.12±11.76 | **<0.001** | 38.82±12.61 | 30.81±10.57 | **<0.001** |
| Ao BP mean, mmhg | 90.40±13.66 | 87.04±16.69 | 0.381 | 95.57±19.15 | 93.72±17.93 | 0.426 |
| RA mean, mmhg | 13.40±4.08 | 9.76±4.56 | **0.003** | 7.09±3.02 | 7.15±3.07 | 0.917 |
| PCWP, mmhg | 9.96±2.60 | 11.32±3.65 | 0.055 | 11.23±3.52 | 11.49±2.95 | 0.413 |
| CI, L/min/m2 | 2.29±0.52 | 2.71±0.67 | **0.025** | 2.62±0.64 | 2.65±0.59 | 0.767 |
| PVR, woods | 11.36±5.15 | 5.46±3.30 | **<0.001** | 6.33±3.65 | 4.09±2.31 | **<0.001** |
| SaPO2, % | 93.08±3.67 | 93.50±3.64 | 0.491 | 93.63±3.81 | 94.78±3.54 | 0.028 |
| PaO2, % | 58.41±11.13 | 65.29±8.48 | 0.004 | 65.68±6.85 | 65.83±7.29 | 0.896 |

*Values are mean ± standard deviation or number, unless specified otherwise.*
** median (interquartile range, IQR)*
*Ao: Aortic; BMI: Body Mass Index; BNP: B-type Natriuretic Peptide; BP: Blood Pressure; CI: Cardiac Index; Hb: Hemoglobin; mPAP: Mean Pulmonary Artery Pressure; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; PA: Pulmonary Artery; PAWP: Pulmonary Artery Wedge Pressure; PVR: Pulmonary Vascular Resistance; PaO2: Arterial Oxygen Partial Pressure; RA: Right Atrium; RV: Right Ventricle; SaO2: Arterial Oxygen Saturation; sPAP: Systolic Pulmonary Artery Pressure; SVR: Systemic Vascular Resistance.*

***Table III.*** *Demographic and hemodynamic findings of CTEPH patients undergoing PEA surgery and BPA procedure*

| | Patients undergoing PEA (total 58) | | | Patients undergoing BPA (total 42) | | |
|---|---|---|---|---|---|---|
| **Variables** | **With RVEF (12)** | **Without RVEF (46)** | **P Value** | **With RVEF (15)** | **Without RVEF (27)** | **P Value** |
| **Demographic values** | | | | | | |
| Age, years | 50.5(39.77-56.67) | 59.0(50.36-61.1) | 0.064 | 46.50(36.7-59.88) | 57.0(46.5-67.22) | 0.185 |
| BMI, kg./m2 | 27.7(24.54-28.76) | 28.7(27.14-31.18) | 0.610 | 24.97(18.47-30.95) | 27.68(26.09-31.06) | 0.590 |
| Hb, g/dl | 12.05(10.26-14.91) | 13.15(12.46-13.7) | 0.623 | 13.05(11.60-13.66) | 13.1(12.46-14.05) | 0.393 |
| NT-Probnp, ng/L | 2052.5(393.7-6017.8) | 1005.0(886.4-2082.1) | 0.264 | 908.5(361.31-3326) | 510(290.81-2790.8) | 0.208 |
| Creatinin, mg/dl | 0.775(0.63-0.99) | 0.795(0.68-0.88) | 0.417 | 0.80(0.66-1.38) | 0.8(0.52-1.35) | 0.517 |
| NT-proBNP | 287.5(233.3-344.6) | 272.5(236.6-302.9) | 0.417 | 266.0(293.25-392.85) | 266(221.58-342.79) | 0.534 |
| **Hemodynamic parameter** | | | | | | |
| PA mean, mmhg | 57.5(42.13-67.07) | 32.5(31.52-42.27) | **0.001** | 55.5(50.69-60.48) | 40.0(35.28-44.95) | **<0.001** |
| Ao BP mean,mmhg | 92.5(87.69-97.71) | 95(94.84-106.83) | 0.914 | 93.5(83.96-102.21) | 95(80.77-104.05) | 0.864 |
| RA mean, mmhg | 13.0(9.58-16.01) | 6.0(5.96-8.56) | **<0.001** | 14.0(12.1-17.05) | 8.0(6.04-9.01) | **<0.001** |
| PCWP, mmhg | 9.50(7.86-13.22) | 11.0(10.05-16.6) | 0.080 | 9.50(7.26-13.7) | 10.0(9.1-13.46) | 0.097 |
| CI, L/min/m2 | 2.17(1.96-2.72) | 2.43(2.28-2.73) | 0.351 | 2.75(1.92-2.48) | 2.15(2.44-3.11) | **0.017** |
| PVR, woods | 11.80(7.51-14.72) | 4.69(4.31-7.27) | **0.002** | 10.36(6.21-14.20) | 5.90(4.12-9.68) | **0.008** |
| SaPO2 (%) | 95.5(91.89-96.91) | 95(93.28-95.86) | 0.999 | 92.0(90.1-96.24) | 93.0(91.44-96.50) | 0.879 |
| PaO2 (%) | 63.0(54.54-67.85) | 66.0(62.93-68.13) | 0.886 | 59.0(55.25-66.38) | 66.0(58.40-68.44) | 0.10 |

*Values are median (interquartile range, IQR), mean ± standard deviation, or number unless specified otherwise.*
*Ao: Aortic; BMI: Body Mass Index; BNP: B-type Natriuretic Peptide; BP: Blood Pressure; CI: Cardiac Index; Hb: Hemoglobin; HT: Hypertension; COPD: Chronic Obstructive Pulmonary Disease; mPAP: Mean Pulmonary Artery Pressure; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; PA: Pulmonary Artery; PAWP: Pulmonary Artery Wedge Pressure; PVR: Pulmonary Vascular Resistance; PaO2: Arterial Oxygen Partial Pressure; RA: Right Atrium; RV: Right Ventricle; SaO2: Arterial Oxygen Saturation; sPAP: Systolic Pulmonary Artery Pressure; SVR: Systemic Vascular Resistance.*


http://doi.org/10.5472/marumj.1484403
Marmara Med J 2024;37(2): 129-136

Demographic and hemodynamic findings of patients undergoing PEA surgery and BPA procedure according to presence of RVEF is discussed separately in Table III.

There was no significant difference found in NT-proBNP levels and 6MWT between both groups undergoing PEA. When examining hemodynamic parameters of patients undergoing PEA, in the group with RVEF, mPAP was 57.5 mmHg (42.13-67.07), while in the group without RVEF, it was 32.55 mmHg (31.52-42.27) (p: 0.001). PVR was 11.80 woods (7.51-14.72) in the RVEF group, whereas it was 4.69 WU (4.31-7.27) in the group without RVEF (p: 0.002); the mRAP was 13.0 mmHg (9.58-16.01) in the RVEF group, whereas it was 6.0 mmHg (5.96-8.56) in the group without RVEF (p: <0.001).

In patients undergoing BPA, there were no significant differences found in demographic data, NT-proBNP levels, and 6-minute walking distance between both groups, whether they had RVEF or not. However, when examining hemodynamic parameters, significant differences were observed in mPAP, mRAP and PVR in the RVEF group compared to those without RVEF (Table III).

## 4. DISCUSSION

In patients with chronic thromboembolic pulmonary hypertension (CTEPH), increased pulmonary vascular resistance leads to high pressure in the right ventricle, resulting in right ventricular failure. RVEF refers to the inability of the right ventricle to transfer its mechanical energy to stroke volume during contraction. This occurs as energy is dissipated through pulmonary vascular resistance during the trans pulmonary flow of blood. Increased pulmonary vascular resistance is associated with the development of RVEF. Despite correction for many established risk factors, right ventricular energy failure is associated with a two fold increase in PH mortality [9]. This concept was initially studied in the left ventricle but also adapted in PH patients [10,11] and its clinical use has been proposed as non-invasive substitute [12,13].

In our study, a more favourable hemodynamic response was observed in patients with RVEF compared to those without RVEF following pulmonary endarterectomy (PEA) surgery or balloon pulmonary angioplasty (BPA) procedure. Surgical candidates, despite having proximal and adequate amounts of thromboembolic material accessible for surgery, still indicate a higher risk due to the presence of RVEF, which demonstrates the severity of right heart failure and their higher risk profile.

In a retrospective study with a follow-up period of lasting 5 years and comprising a total of 549 pulmonary hypertension patients, with 343 (62%) being patients with CTEPH, RVEF was observed in 146 (26.6%) patients and was shown to predict long-term mortality independently [7]. Our study had a similar frequency of RVEF presence (27%) compared to frequency of RVEF rates reported in previous studies.

In a study conducted by Stefan Guth and his friends between January 2010 and March 2016, prospectively examining the PEA outcomes of 664 CTEPH patients, significant improvement was observed in RHC parameters, WHO Functional Class, and symptoms following PEA. This improvement was shown to persist for one year [14].

Another large prospective study from the United Kingdom national cohort obtained dynamic risk stratification of long term outcome in 880 PEA patients. Significant functional improvement following surgery with 85% of patients in either Functional Class I or II, only 28% of patients had an mPAP ≤20 mm Hg, whereas 51% had an mPAP ≥25 mm Hg when measured by right heart catheterization at 3 to 6 months post-PEA. The majority of deaths following the immediate postoperative period were not attributable to right ventricular failure [15]. Identifying patients with RVEF initially prior to PEA with hemodynamic measurements could be interpreted as high risk patients and this would help to better establish CTEPH related clinical deterioration and the need for reassessment during follow up.

In a cohort study conducted by Reesink et al., between May 2000 and August 2009, evaluating the effects of PEA on 74 patients, the 6MWT was shown to be associated with parameters reflecting the clinical and hemodynamic severity of CTEPH. The average 6MWT was 389 meters initially, which increased to 480 meters at one year of follow-up following PEA [16]. When looking at 6MWT and NT-ProBNP levels used in risk classification of CTEPH patients, an increase in 6MWT distance and a decrease in NT-ProBNP levels were found to be statistically significant. The correlation observed in both groups, those with and without RVEF, supported the findings of previous studies and similar hemodynamic improvements were observed in our study, consistent with previous findings.

In a prospective study evaluating the effect of PEA on pulmonary hemodynamics in 32 CTEPH patients, right heart catheterization findings were assessed 12 months post-PEA, showing a lower mPAP (20±3 vs. 17±3 mmHg; p=0.008) and a decrease in PVR from 3.6±0.8 WU preoperatively to 2.7±0.7 WU post-PEA (p=0.004) [17].

In another study, a cohort study conducted in the United Kingdom involving 880 CTEPH patients, during the 3-6 month assessment following PEA, it was observed that 28% had mPAP < 20 mm Hg and 21% had mPAP 21-24 mm Hg, and this decrease was found to be statistically significant [18].

Pulmonary endarterectomy surgery and BPA procedures have been shown to result in a significant decrease in right ventricular afterload and contribute to the improvement of right ventricular function, while also positively impacting right ventricular contractile function. In our study, both groups exhibited positive improvement in hemodynamic parameters; however, patients with RVEF experienced higher risks associated with the procedure but at the same time benefited more when compared to patients without RVEF.

Additionally, patients with RVEF showed a significant increase in cardiac output (CO) and cardiac index (CI) ( p: 0.030 and p: 0.025 respectively ), whereas in the non-RVEF group, although, an increase was observed, it did not reach statistical significance. This could be due to the relatively near normal and better values observed in patients without RVEF group already before PEA or BPA procedure.


http://doi.org/10.5472/marumj.1484403
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In many European centers, a study examining the results of BPA procedures revealed that the decrease in mPAP is generally below 30%, and according to recently published global registry data, a 41.5% reduction in PVR was observed in Europe. In two centers in Germany, a total of 266 BPA sessions were conducted in 56 patients, resulting in an 18% decrease in mPAP and a 26% decrease in PVR. The results in our study were consistent with the findings of previous studies yet another study conducted in Japan with 7 BPA centers reported a higher BPA effectiveness with a 47.9% decrease in mPAP [19].

The significant decrease in mean pulmonary artery pressure and pulmonary vascular resistance, regardless of the presence of RVEF, indicates a reduction in right heart pressure load. However, there were differences observed in CO and CI depending on the presence of RVEF. In our study, there was no significant difference in the non-RVEF group after PEA and BPA procedures, which contradicts previous studies. Mizoguchi et al., examined the results of BPA procedures in Japan and reported significant improvement in CO and CI [20].

A relatively short duration of follow up period in our study may not adequately reflect the effect of PEA and BPA procedures on CO and CI. The discrepancy finding in our study may be explained by the relatively normal range of CO and CI values in the non-RVEF group (CO, 4.86 ± 1.29 L/min and CI, 2.62 ± 0.64 L/min/m2).

### Study limitations

Although, our study conducted at a tertiary center specialized in CTEPH, being a single – center is the primary limiting factor. Variations in follow-up periods occurred due to some patients unable to reach hospital after follow-up visit schedule was arranged. Some patients who underwent BPA had previously undergone pulmonary endarterectomy but were complex cases that did not respond to treatment; therefore, only a limited number of interventions could be performed, and these patients were excluded from the study. Finally, larger and with a longer period of follow-up prospective studies are needed to effectively establish the significance of RVEF in the hemodynamic and long term clinical outcome after treatment in this group.

### Conclusion

In conclusion, the presence of RVEF, a high-risk factor for long-term survival and development of heart failure in pulmonary hypertension, did not negatively affect the outcomes of PEA or BPA procedures. A significant hemodynamic and clinical improvement during the medium-term follow-up was achieved without increasing risk of complication in the perioperative early period and this improvement was consistently observed in patients undergoing both treatment strategies.

### Compliance with Ethical Standards

**Ethical approval**: Ethical approval for the study was obtained from the Clinical Research Ethics Board (18.04.2023 approval number: 09.2023.309), and the study was conducted in accordance with the Helsinki Declaration.

**Funding**: The authors declared that this study has received no financial support.

**Conflict of interest**: The authors declare that they have no conflict of interest.

**Author contributions:** RSB, HA and EG: Conceived the original idea. This was also discussed with BM, DA and BY. All authors discussed and agreed with the main focus and idea of this paper. The main ideas behind this paper were conceived by HA, EA and RSB with many helpful suggestions from BM.

BY together with BM conceptualized this study, generated population and contriubed data and analysis tool. Data was mainly collected by RSB and HA helped in performing data analysis. The main text of the paper was written by RSB and subsequently improved by HA and DA helped edit the manuscript.

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