Original Article

Clinical and physiological characteristics of, medically treated, chronic thromboembolic pulmonary hypertension patients in Saudi Arabia: A single center experience

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Abstract:

BACKGROUND: Chronic thromboembolic pulmonary hypertension (CTEPH) is uncommon but well-known sequel of venous thromboembolism (VTE). At present, it is the only potential curable subtype of pulmonary hypertension. The aim of this study is to describe the medically treated-CTEPH patients' characteristics in a single specialized PH center in Saudi Arabia.

METHODS: This study presents demographic, clinical, physiological, and hemodynamic characteristics of medically treated-CTEPH patients in a single PH center, namely Prince Sultan Military Medical City, Riyadh, Saudi Arabia. Both incident and prevalent cases are included.

RESULTS: A total of 20 patients with a confirmed diagnosis of CTEPH were included. Mean age at diagnosis was 43 years with a female preponderance of 75%. Most common presenting symptom was dyspnea (100%) followed by syncope (58%). At diagnosis, a mean of 15 ± 10 months had passed since symptoms onset. About 45% of patients were in WHO functional class IV. At baseline, mean 6-min walk distance was 354.3 meters. Overall, VTE was the most frequent risk factor identified (65% of all patients). Nearly 30% of patients had sickle cell disease. 13 out of 20 patients had radiographic (i.e., computed tomography [CT] pulmonary angiogram) features of chronic thromboembolism. About 75% of patients were found to have distal disease on radiographic imaging. At the time of diagnosis, 7 out of 20 (35%) patients demonstrated right ventricular failure on echocardiography. Mean tricuspid annular plane systolic excursion was 17.7 ± 1.20. Median NT-proBNP levels were found to be 688 pg/ml. Mean diffusing capacity for carbon monoxide was 74.8%.

CONCLUSIONS: Diagnosis of CTEPH was established at a relatively younger age. Majority of patients had advanced but distal disease on radiographic imaging, not amenable to surgery.

Keywords:

Chronic thromboembolic pulmonary hypertension, echocardiography, pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating disease with high morbidity and mortality if left untreated.[1] Theoretically, it is considered as a consequence of incomplete thrombus resolution after an acute or recurrent pulmonary embolism which leads to organization and progressive fibrotic obliteration of proximal pulmonary arteries as well as vascular remodeling in distal vasculature.[2] Consequently, this leads to rise in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) culminating in right heart failure and death.

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CTEPH is defined as precapillary PH (mean PAP >20 mmHg and pulmonary capillary wedge pressure [PCWP] ≤15 mmHg) in the presence of at least one mismatched segmental perfusion defect on ventilation/perfusion (V/Q) scan. As opposed to CTEPH, chronic thromboembolic disease (CTED) refers to patients with persistent symptoms and mismatched perfusion defects in the absence of resting PH on invasive hemodynamic study.[3]

Incidence of CTEPH remains uncertain, however, large prospective cohort studies and international registries report an incidence of 0.56%–6.2%.[4-7] Recurrent pulmonary embolism, idiopathic venous thromboembolism (VTE), and right ventricular (RV) dysfunction at presentation are associated with higher risk of CTEPH.[4,8,9]

Despite being a well-recognized complication of acute VTE, CTEPH remains underdiagnosed.[9,10] Delayed referral, misdiagnosis, and lack of antecedent history of pulmonary embolism in a significant proportion of patients lead to delay in CTEPH diagnosis with catastrophic outcomes for patients.[11,12] This is of particular concern since, unlike other subgroups of PH, CTEPH is amenable to surgical intervention. Pulmonary endarterectomy (PEA) is the standard of care in eligible, operable, patients with reported 3-year survival of 90%.[13,14] A multitude of host and disease-related factors which include comorbidities and confinement of disease to distal vasculature may render as many as 40% of patients inoperable.[14] Despite being potentially curative, up to one-third of patients may have residual PH post-PEA.[15] Last several years have witnessed significant advancements in the management of inoperable or residual PH including medical therapy and balloon pulmonary angioplasty.[16]

Although large international registries have elucidated epidemiology and optimal management of CTEPH patients, significant heterogeneity exists in demographic and clinical characteristics of local resident population as well as available treatment options. Little data have been reported in regard to CTEPH prevalence and disease and patients' specific characteristics from the Kingdom of Saudi Arabia. This study aims to describe baseline characteristics of, medically treated, CTEPH patients in a single center in Saudi Arabia.

Methods

Study design

This is a retrospective, analytical study focused on suspected and confirmed CTEPH patients referred to Prince Sultan Military Medical City (PSMMC), a tertiary care PH specialized center, over a 9-year period.

Study protocol was reviewed and approved by the Research and Ethics Committee of Prince Sultan Military Medical City.

Participants

Patients with newly diagnosed (incident) or previously diagnosed (prevalent) CTEPH were included in the study. Diagnosis was established through right heart catheterization (RHC).

Diagnostic criteria included mPAP >20 mmHg and PCWP ≤15 mmHg, on invasive hemodynamic assessment (RHC), in the presence of mismatched perfusion defects on V/Q scan or presence of specific diagnostic multidetector CT, or conventional pulmonary angiographic signs of chronic thrombotic vascular material (webs, slits, ring-like stenoses, pouches, tortuous lesion, or total vascular occlusion).

All patients (older than 14 years of age) with above-mentioned diagnostic criteria were enrolled in the study between January 2011 and December 2019. Patients with other types of precapillary PH (WHO Groups I, III, and V) were excluded from the study.

Data collection

Patients' data were collected retrospectively through electronic medical records. Baseline assessment including history and clinical examination was documented for all suspected and diagnosed cases. Medical history included onset of symptoms, time of diagnosis (prevalent cases), WHO functional class at baseline, body mass index (BMI), comorbidities and risk factors for CTEPH, and clinical diagnosis of right heart failure at presentation. Diagnostic tests including autoimmune profile, sickle cell disease (SCD) screen, imaging studies, such as VQ scan and CT pulmonary angiogram (CTPA), and pulmonary function tests with diffusing capacity for carbon monoxide (DLCO) were documented for all patients at baseline.

Data for objective physiological assessment were collected for all patients at the time of referral/diagnosis with NT-proBNP, 6-min walk distance (6MWD), and 2D echocardiographic parameters (RV function tricuspid annular plane systolic excursion [TAPSE]), pericardial effusion, TRVmax, and RV dilatation). Hemodynamic assessment through RHC including mPAP, right atrial pressure (RAP), cardiac index (CI), PCWP, and PVR was done for all enrolled patients.

All patients received standard clinical care according to ESC/ERS guidelines during the period of study.

Statistical analysis

Descriptive statistics were used to summarize demographic and other clinical, radiological, and laboratory

characteristics of the participants. Categorical variables were expressed as frequencies and percentages (%), whereas continuous variables were presented as means ± standard deviations (SDs) when data were normally distributed or as median and interquartile range if data were skewed. Student's *t*-test and ANOVA test were used for continuous variables with normal distribution, and Chi-squared test was used for comparison of categorical variables. A $P < 0.05$ was considered statistically significant. SPSS version 25; July 2017; Armonk, NY; IBM Corp was used for statistical analysis.

Results

Study population

A total of 27 patients with clinically suspected WHO Group IV PH were referred to PSMMC PH clinic between January 2011 and December 2019. Of these, 20 (74%) patients met eligibility criteria for enrolment. All patients in study population were incident cases. Four patients received a final diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH) hence excluded from the study. Three patients were not found to have PH on RHC despite abnormal VQ scan and echocardiography. Therefore, they were analyzed separately as a distinct group labeled as CTED. Figure 1 illustrates distribution of the study cohort.

Demographics

Mean age at diagnosis was 43 (±13) years. Of 20 patients, 75% were female. All patients were Saudi. Ten out of 20 patients (50%) were from central province.

Baseline clinical characteristics

At baseline, most patients belonged to WHO functional classes III (45%) and IV (40%) while only 15% were in functional class II. Majority of patients were overweight with mean (±SD) BMI was 31 (±7.5). All patients were symptomatic at the time of diagnosis with dyspnea being the most common symptom (100%) followed by syncope (55%) and palpitations (30%), while 4 (20%) patients had clinically evident right heart failure. Mean (±SD) time from symptom onset to diagnosis was 15 (±10) months. Table 1 describes risk factors and comorbidities of both CTEPH and CTED patients. Overall, 80% of patients in study cohort had one or more known risk factors for CTEPH.

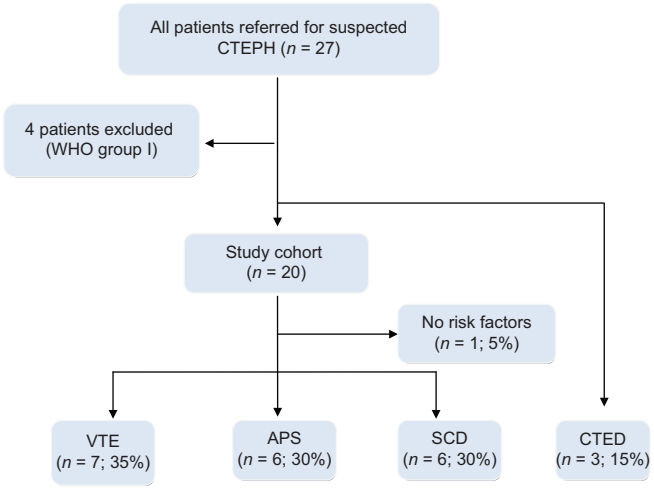

Figure 1: Distribution of study cohort. CTEPH=Chronic thromboembolic pulmonary hypertension, RHC=Right heart catheterization, CTED=Chronic thromboembolic disease, WHO=World Health Organization, VTE=Venous thromboembolism, APS=Antiphospholipid syndrome, SCD=Sickle cell disease

Physiological and hemodynamic characteristics

Baseline exercise capacity with 6MWD (± SD) was 354.3 (±93.2) meter. Median NT-proBNP levels were found to be higher (688 pg/ml) in 94% of patients. Cardiopulmonary exercise testing was not performed in any patient. Pulmonary function tests were available for 10 patients (52%) with mean DLCO of 74.8 (±7).

Baseline echocardiography was available for all patients which revealed elevated mean systolic pulmonary artery pressure (sPAP) of 67 (±5.5) mmHg, tricuspid regurgitation maximum velocity (TRVmax) of 3.55 (±0.17) m/s, while half (55%) patients had moderate-to-severe RV dilatation (RV inlet in four-chamber view). Baseline TAPSE score was available in 14 patients with mean value of 17.7 (±1.20) mm. About 40% of patients had evidence of reduced systolic function and half of these patients had presence of pericardial effusion.

RHC was performed on all patients at baseline. Mean PAP was elevated at 42 (±3.1) mmHg; RAP 8 (4–13) mmHg; PCWP 11 (±0.90) mmHg; PVR of 9.4 (±2) woods units; CI of 2.6 (±0.2) $L/min^{-1}/m^{-2}$; and mixed venous saturation (SvO2%) in pulmonary artery was 64% (±2.6%).

Table 1: Risk factors and comorbidities of chronic thromboembolic pulmonary hypertension and chronic thromboembolic disease patients

Risk factors	CTEPH (*n*=20), *n* (%)	CTED (*n*=3), *n* (%)
Venous thromboembolism	7 (35)	3 (100)
Recurrent PE	6 (85)	-
Thrombolysis	3 (43)	3 (100)
Primary or secondary APS	6 (30)	-
Sickle cell disease	6 (30)	-
Obesity	12 (65)	-
Hypertension	7 (35)	2 (67)
Diabetes	6 (30)	2 (67)
Splenectomy	3 (15)	-
Hypothyroidism	3 (15)	-
COPD	2 (10)	-
SLE	3 (15)	-

CTEPH=Chronic thromboembolic pulmonary hypertension, CTED=Chronic thromboembolic disease, APS=Antiphospholipid syndrome, PE=Pulmonary embolism, COPD=Chronic obstructive pulmonary disease, SLE=Systemic lupus erythematosus

Ventilation perfusion scan was available for 90% of patients showing multiple mismatched perfusion defects. For the 2 patients who lacked perfusion scan, they underwent conventional pulmonary angiography which confirmed multiple proximal and segmental filling defects. Table 2 presents baseline clinical and hemodynamic characteristics of study population according to functional class.

Traditional invasive pulmonary angiography was not a part of routine assessment at the time of enrolment, however, CTPA was done for all patients as part of workup. Dilated pulmonary trunk (>3 cm) and bilateral mosaic attenuation were the most frequent CTPA findings seen in almost all patients (95%). RV strain as evidenced by RV/LV ratio >1 and interventricular septal bowing toward left ventricle was observed in 7 out of 20 patients (35%). Characteristic CTEPH features on CT scan such as intraluminal fibrous bands/webs and stenoses with bronchial artery collaterals were identified in majority of patients (60%) while one patient had complete absence of perfusion in left lung due to total occlusion of left pulmonary artery. Nearly 75% of study cohort had evidence of predominantly distal disease on CTPA with only 2 patients showing surgically accessible proximal thrombi.

About 30% of CTEPH patients had SCD. In a subgroup analysis, 5 out of 6 SCD patients were female and had lower BMI (25) than rest of the patients. All 6 patients were symptomatic and belonged to WHO functional class III/IV. No statistically significant difference in mean age, symptom duration, physiological (6MWD and NT-proBNP), and echocardiographic (TRVmax and TAPSE) characteristics was seen between SCD and rest of CTEPH patients. Hemodynamically, a lower mean PAP (36 mmHg) and PVR (4.8 WU) with slightly higher CO (5.4 L/min) was seen in SCD patients but results did not achieve statistical significance.

Of 27 patients referred to our center for expert evaluation, 3 were found to have persistent dyspnea on exertion (WHO functional class II/III) and multiple mismatched perfusion defects in VQ scan despite 3–6 months of anticoagulation. Mean duration of symptoms was 14 months from index VTE event. They had been diagnosed with massive PE and received thrombolytic treatment. All of them had abnormal echocardiograms (mean sPAP – 41 mmHg, mean TAPSE score – 21 mm, and TRVmax – 2.8 m/s) but normal NT-proBNP (mean 41 pg/ml) and RHC at rest. Functional assessment with 6MWD and cardiopulmonary exercise test was not available for CTED patients.

Table 3 discusses clinical and hemodynamic data of all patients and subgroups.

Discussion

The present study highlights the findings of a small cohort of consecutive CTEPH and CTED cases referred to and diagnosed at a single specialist center in Saudi Arabia. The diagnosis was confirmed with RHC. The main aim of this study is to describe the disease at presentation utilizing demographic and clinical profiles of incident medically treated-CTEPH cases. A clear female preponderance was seen in our cohort with a significantly lower mean age at diagnosis (44 years) than the mean age reported internationally.[12,17-19] However, our findings are in line with previously reported data

Table 2: Baseline clinical and hemodynamic characteristics of chronic thromboembolic pulmonary hypertension population according to World Health Organization functional class

Variables	Total	WHO FC II	WHO FC III	WHO FC IV	*P*
Number of patients	20	2	9	9	
Age (years)	43.2 (±13.2)	48.5 (±6.36)	39.4 (±10.2)	45.7 (±16.5)	0.5
Gender, *n* (%)					
Female	15 (75)	0	8 (88.9)	7 (77.8)	0.03
Male	5 (25)	2 (100)	1 (11.1)	2 (22.2)	
BMI	31.1 (±7.5)	32.35 (±6.1)	29.9 (±7.5)	32.14 (±8.4)	0.8
Symptoms duration (month)	14.8 (±9.8)	24 (0)	14.1 (±10)	13.5 (±10.4)	0.4
Syncope, *n* (%)	11 (55)	1 (9)	5 (45.4)	5 (45.4)	0.9
6MWD (m)	354.3 (±93.2)	396 (0)	340.8 (±48.3)	347 (±173.9)	0.9
NT-proBNP (pg/mL)	688 (81-2657)	12.5 (12-13)	162 (108-695)	2629.5 (1095-6616.5)	0.08
TAPSE (mm)	17.7 (±1.20)	20	19 (±2.99)	17.3 (±0.91)	0.7
RAP (mmHg)	8.3 (±3.04)	10	8.25 (±3.2)	8.14 (±3.2)	0.8
mPAP (mmHg)	42 (±12.8)	44	42.1 (±13.3)	41.5 (±14.3)	0.9
PVR (WU)	9.15 (±1.88)	4	9.52 (±2.7)	9.42 (±3.09)	0.9
CI (L/min/m^2)	2.63 (±0.2)	3.1	2.7 (±0.26)	2.48 (±0.32)	0.7

WHO=World Health Organization, FC=Functional class, BMI=Body mass index, 6MWD=Six-min walk distance, RAP=Right atrial pressure, PVR=Pulmonary vascular resistance, NT-proBNP=N-terminal pro-B-type natriuretic peptide, TAPSE=Tricuspid annular plane systolic excursion, mPAP=Mean pulmonary arterial pressure, CI=Cardiac index

of local pulmonary arterial hypertension and CTEPH population.[20,21]

Another important clinical finding from our data points to the fact that despite younger age, CTEPH patients are diagnosed late in the course of the disease. Upon presentation, most of our patients had advanced disease as evident by several clinical and hemodynamic parameters, such as higher functional class III/IV and symptom burden, high NT-proBNP, RAP, mPAP, and PVR, as well as low CI and 6MWD, indicating worse prognosis.[13] This could partly be attributed to diagnostic delay (mean duration 15 months from onset of symptoms to confirmation of diagnosis). Both international and local studies have associated diagnostic delay with worse hemodynamic profile and shorter survival.[11,12,20,21]

Consistent with previous studies,[9,12,19,20] VTE (with or without concomitant risk factors, such as antiphospholipid syndrome or SCD) was the major risk factor identified in our CTEPH cohort (65%). Although only one of our patients had no evidence of a previous symptomatic thromboembolic event, up to 25% of patients may have no prior history of VTE,[12] which makes an early diagnosis of CTEPH challenging. Among those with a history of VTE, the majority had evidence of recurrent PE but only 3 patients had received thrombolytic treatment in the past. Both recurrent and massive PE are shown to be independent risk factors for the development of CTEPH[7,12] and may aid clinicians to identify patients at high risk of developing CTEPH.

SCD was another remarkable comorbidity identified in our CTEPH patients. PH in SCD (PH-SCD) is multifactorial and is currently classified as Group V pulmonary hypertension.[22] The prevalence of RHC confirmed PH-SCD is 6%–10% but is likely to be underestimated. Nevertheless, it is a devastating complication of SCD and an independent predictor of mortality.[23-25] Both pre and postcapillary PH are seen in PH-SCD, however, the precapillary component has been reported to be slightly more prevalent in previous studies[26,27] and is associated with poor prognosis.[26,28] Chronic thromboembolism and intravascular hemolysis leading to nitric oxide depletion and endothelial dysfunction are major contributors to precapillary PH-SCD. A recent study has shown a high prevalence of mismatched segmental perfusion defects in VQ scintigraphy and advocates the use of VQ scan for CTEPH screening in this population.[28]

Baseline characteristics of our SCD cohort did not differ significantly from other CTEPH patients. All of them were in WHO functional classes III-IV signifying advanced disease and high symptom burden. All six SCD patients in our CTEPH cohort had abnormal VQ scan, highly suggestive of CTED. mPAP and PVR of SCD patients were lower than the mPAP and PVR of the CTEPH cohort, but with elevated CO, findings are well explained by underlying pathophysiology of PH-SCD and have been reported previously.[26-28] Despite seemingly milder elevations in pulmonary pressures, SCD patients have poor functional status and higher mortality. Therefore, any modifiable risk factors or redeemable pathology such as CTEPH should be actively sought and managed in these patients. PEA is a potentially curative surgery, which has recently been offered to SCD patients with CTEPH and found to be safe with comparable results with those reported for other CTEPH patients.[29]

Table 3: Clinical and hemodynamic data of all patients and subgroups

Variables	VTE (*n*=7)	APS (*n*=6)	SCD (*n*=6)	*P*
Age (years)	51.5 (±16.4)	38.1 (±6.6)	39.3 (±12.1)	0.13
Gender, *n* (%)				
Female	4 (57)	5 (83)	5 (83)	0.4
Male	3 (43)	1 (17)	1 (17)	
BMI	32.6 (±6.7)	34.5 (±8.1)	25.6 (±6.4)	0.1
Symptoms duration (months)	21.7 (±13.2)	9.5 (±4)	13 (±5.8)	0.06
WHO FC IV, *n* (%)	3 (43)	5 (83)	2 (33)	
6MWD (m)	351 (±63.2)	347 (±174)	375	0.9
NT-proBNP (pg/mL)	420 (108-695)	2657 (1502-19835)	162 (13-10000)	0.2
TAPSE (mm)	16.9 (±3.6)	18.8 (±5.9)	20.6 (±1.74)	0.4
RAP (mmHg)	10.5 (±3.9)	5.5 (±3)	8.4 (±2.4)	0.08
mPAP (mmHg)	44.5 (±13.3)	39.7 (±15.7)	36.6 (±5.7)	0.5
PCWP (mmHg)	13 (±3.2)	9.2 (±2.5)	12.3 (±4.6)	0.2
PVR (WU)	11.2 (±9.4)	10.8 (±10)	4.8 (±1.5)	0.2
CO (L/min)	4.7 (±1.8)	4 (±1.5)	5.3 (±1.1)	0.3
CI (L/min/m^2)	2.4 (±0.7)	2.3 (±0.8)	3.2 (±0.5)	0.07

WHO=World Health Organization, FC=Functional class, BMI=Body mass index, 6MWD=Six-min walk distance, RAP=Right atrial pressure, PVR=Pulmonary vascular resistance, mPAP=Mean pulmonary arterial pressure, PVR=Pulmonary vascular resistance, CO=Cardiac output, CI=Cardiac index, VTE=Venous thromboembolism, APS=Antiphospholipid syndrome, SCD=Sickle cell disease

Three patients referred to our center for expert evaluation had persistent dyspnea and poor exercise tolerance with abnormal perfusion defects and echocardiographic findings of elevated sPAP but normal RHC at rest (CTED). Their baseline clinical and radiological characteristics did not differ significantly from our CTEPH patients. Interestingly, all 3 patients had a history of massive PE and had received thrombolytic treatment in the past. Post-PE syndrome or CTED has been well described in the literature.[3,30] The etiology and prevalence of this entity are not fully known since persistent symptoms, and perfusion defects are not uncommon post-PE.[31] Reduced pulmonary blood flow and increased dead space ventilation leading to VQ mismatch during exercise are the postulated mechanism for CTED.[32] In recent years, PEA has been performed for this group of patients with the aim to reduce symptom burden and improve quality of life. Two recent studies[30,33] have looked at the postsurgical outcome of CTED patients and have been shown to be safe and comparable to CTEPH. Although we identified 3 patients, actual number is likely to be underestimated due to a lack of awareness for this entity in general practice.

Our study had several limitations. The main limitation was a small group of patients which affected the statistical analysis. Second, data were collected retrospectively which led to retrieval bias. Although hemodynamic data were retrieved for all patients, certain physiological parameters such as 6MWD, TAPSE, and DLCO were not available for some patients.

Conclusions

In conclusion, our study echoes previously reported findings from Saudi Arabia of a younger CTEPH population with advanced disease at presentation suggesting diagnostic delay. The majority of patients were found to have a distal disease on radiological evaluation.

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Conflicts of interest
There are no conflicts of interest.

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