Indian Heart Journal 73 (2021) 746–750

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Research Brief

Incidence and predictors of chronic thromboembolic pulmonary hypertension following acute pulmonary embolism: An echocardiography guided approach

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ARTICLE INFO

Article history:
Received 1 January 2021
Accepted 19 October 2021
Available online 21 October 2021

Keywords:
Computed tomographic pulmonary angiogram
Echocardiogram
Ventilation-perfusion scan

abstract

There is significant variability in the worldwide epidemiology of chronic thromboembolic pulmonary hypertension (CTEPH). We thereby aim to determine the incidence and predictors of CTEPH, following an episode of acute pulmonary embolism (PE), using non-invasive modalities. Patients with acute PE were prospectively followed-up and after receiving at least 3 months of effective anticoagulation, persistently symptomatic patients with echocardiographic evidence of persistent pulmonary hypertension, were investigated further for CTEPH. Incidence of CTEPH was 8.19%. Delayed presentation, higher pulmonary artery pressures at presentation and discharge, and greater thrombotic burden were significant predictors for the development of CTEPH following acute PE.

1. Introduction

Determining the precise incidence of Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is complex. CTEPH is conventionally diagnosed when despite effective anticoagulation for 3 months, the mean pulmonary artery pressure remains >20 mm Hg as documented at right heart catheterisation (RHC), along with mismatched perfusion defects on ventilation-perfusion (V/Q) scan.[1] Confirmation of CTEPH by RHC becomes challenging sometimes, particularly in a resource limited developing country like India. Therefore, simpler and inexpensive methods are needed to diagnose this curable entity at an earlier stage.

2. Methods

Design: Single centre, prospective follow-up study.
Objectives:

- To determine the incidence of CTEPH, following an episode of acute pulmonary embolism (PE), using echocardiography, V/Q scan and computed tomographic pulmonary angiography (CTPAG).
- To determine the factors predictive of development of CTEPH.

All patients admitted with acute PE were included, but patients with co-existing congenital or acquired heart disease, co-existing lung disease, patients with HIV infection and patients with pre-existing CTEPH were excluded.

Informed consent was obtained from all patients. The study conforms to widely accepted ethical principles guiding human research (such as the Declaration of Helsinki) and was approved by the institutional Ethics Committee.

Patients with acute PE were stratified into risk categories based on the BOVA risk score.[2] Intermediate-high risk cases were thrombolysed with either streptokinase or tenecteplase and intermediate-low risk & low risk cases were kept on parenteral anti-coagulation only.

Echocardiography was used to measure the baseline pulmonary artery systolic pressure (PASP) for all patients at the time of admission and at discharge.

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https://doi.org/10.1016/j.ihj.2021.10.003

Abbreviations

CTEPH	Chronic Thromboembolic Pulmonary Hypertension
RHC	Right Heart Catheterization
V/Q	Ventilation-Perfusion
PE	Pulmonary Embolism
CTPAG	Computed Tomographic Pulmonar Angiogram/ Angiography
PASP	pulmonary artery systolic pressure
VKA	Vitamin K antagonists
PH	Pulmonary Hypertension
CI	Confidence Interval
DVT	Deep Vein Thrombosis

All patients were discharged on oral anticoagulation either with a Vitamin K Antagonist (VKA) (target INR of 2–3) or on Dabigatran (150 mg bid). Meticulous follow-up was ensured to maintain effective anti-coagulation.

After at least 3 months of effective anti-coagulation, patients with persistent symptoms, underwent echocardiography to look for features of persistent pulmonary hypertension (PH).[3] V/Q scan was used for screening and CTPAG was used to confirm CTEPH in cases with persistent symptomatic PH.

Statistical analysis: Per protocol analysis was used: only those patients who had received at least 3 months of effective anti-coagulation, were followed-up and the results analysed.

Pearson's Chi-square test was predominantly used (Fischer's exact test, when cell size was <5).

Statistical Software: SPSS-Version 22.0.

'p' value < 0.05 was considered significant

Z for 95% confidence interval (CI) = 1.96.

3. Results

From October 2017 to October 2018, 304 patients with acute PE were recruited, 84 died during the initial admission or were lost to follow-up, resulting in 220 patients with effective anti-coagulation.

Demographic details of all eligible patients have been shown in Table 1.

101 patients had persistent symptoms on follow-up, but only 21 had features of persistent PH on echocardiography. 18 of these 21 cases had CTEPH.

Incidence of CTEPH following an episode of acute PE was 8.19% (95% CI 2.6–13.7%)

Delayed presentation (symptom duration >7 days), higher PASP at admission and discharge, and a greater thrombotic burden were associated with higher likelihood of development of CTEPH (Table 2).

4. Discussion

The exact incidence of CTEPH in patients who have suffered acute PE is debated and there has been a lacunae for the same from the Indian subcontinent. In published prospective studies with diagnosis confirmed by RHC, the incidence of CTEPH after symptomatic acute PE is reported to range from 0.4% to 6.2%, giving a pooled incidence of 3.4%.[4] The incidence of CTEPH following the first episode of acute PE was reported to be as high as 20% in an Indian study, but most of these patients had ineffective anti-coagulation.[5] The higher incidence (8.19%) of CTEPH in our study can be attributed to referral bias, as mostly intermediate-high risk cases of PE are referred to our centre, and also to the fact that our patients present late.

In our study, the mean age of patients diagnosed to have CTEPH was 51.83 ± 4.24 years, in contrast to 63 years in the international CTEPH registry.[6]

Table 1
Demographic details of all eligible patients with acute PE.

S.No	Parameter		N-220 (%)
1	Age (years)	mean ± SD	44.42 ± 3.34
2	Sex	Male	124 (56.36)
		Female	96 (43.64)
3	Smoking	Yes	116 (52.73)
		No	104 (47.27)
4	BOVA risk score	>4 (intermediate-high risk PE)	123 (55.91)
		3-4 (intermediate-low risk PE)	58 (26.36)
		<2 (low risk PE)	39 (17.73)
5	Co-existing DVT	Yes	99 (45)
		No	121 (55)
6	RV dysfunction at presentation	Yes	123 (55.91)
		No	97 (44.09)
7	PASP at presentation	>50 mm Hg	112 (50.91)
		≤50 mm Hg	108 (49.09)

PE: Pulmonary Embolism.
DVT: Deep Vein Thrombosis.
RV: Right Ventricle.
PASP: Pulmonary Artery Systolic Pressure.

Table 2
Summary of analysis of all the factors assessed for CTEPH.

Factor	CTEPH		p value	Odds ratio
	Yes	no		
Smoking			0.45	**0.18 (95% CI 0.78–1.74)**
Yes	11	105		
No	7	97		
Co-existing DVT			0.05	**2.64 (95% CI 0.95–7.32)**
Yes	12	87		
No	6	115		
Thrombolytic agent			0.18	**2.57 (95% CI 0.54–12.20)**
Streptokinase	11	75		
Tenecteplase	2	35		
Duration of symptoms			0.0001	**7.31 (95% CI 2.48–21.48)**
>7 days	13	53		
<7 days	5	149		
PASP at initial presentation			0.014	**3.71 (95% CI 1.18–11.67)**
>50 mm Hg	14	98		
≤50 mm Hg	4	104		
RV dysfunction at initial presentation			0.11	**2.18 (95% CI 0.75–6.33)**
Yes	13	110		
No	5	92		
PASP at discharge			0.029	**3.11 (95% CI 1.07–9.04)**
>40 mm Hg	13	92		
≤40 mm Hg	5	110		
Follow-up Anti-coagulation			0.17	**1.98 (95% CI 0.63–6.24)**
Vitamin K antagonist	14	129		
Dabigatran	4	73		
Visible Thrombus in main and/or branch pulmonary arteries (right or left pulmonary artery)			0.004	**4.67 (95% CI 1.47–14.55)**
Yes	14	87		
No	4	115		

CTEPH: Chronic Thromboembolic Pulmonary Hypertension.
DVT: Deep Vein Thrombosis.
PASP: Pulmonary Artery Systolic Pressure.
RV: Right Ventricle.

We found that systemic thrombolysis was not a deterrent for subsequent development of CTEPH. Similar findings were demonstrated in the 3-year follow-up of the PEITHO trial.[7]

Consistent with previous reports,[6,8,9] our study also showed that delayed presentation, higher PASP at admission and discharge and greater thrombotic burden, were associated with higher likelihood of development of CTEPH.

Ideally, diagnosis of PH requires RHC, but, echocardiography can also be a reasonable tool to identify such patients.[3] In the REVEAL registry, echocardiographic measures of PH correlated with findings on RHC in up to 80% patients.[10]

V/Q scanning is a safe and highly sensitive screening test for CTEPH. A normal scan essentially excludes the diagnosis.[11] Worsley et al[12] and Tunariu et al[13] demonstrated a sensitivity of V/Q scan approaching 100% and 96–97% respectively.

CTPAG has also shown consistently high sensitivity and specificity of up to 98.3 and 97% for detecting CTEPH at main/lobar levels and up to 94 and 95% at segmental levels, respectively.[14,15] However, CTPAG might underestimate CTEPH confined to distal pulmonary arteries.[16]

A subsequent study by He and colleagues showed a more favourable comparison between the two techniques with V/Q sensitivity, specificity, and accuracy of 100, 93.7, and 96.5% (high and intermediate probability scintigraphy); 96.1, 95.2, and 95.6%, respectively (high-probability scintigraphy); and CTPAG sensitivity, specificity, and accuracy of 92.2, 95.2, and 93.9%, respectively.[17]

CTPAG thus complements the information obtained from V/Q scan and the combination of echocardiography, V/Q scan and CTPAG provides a cost-effective, non-invasive and simpler approach to diagnose CTEPH, avoiding the risks and delay associated with invasive assessment.

A simplified diagnostic algorithm to CTEPH is shown in Fig. 1.[18]

4.1. Limitations

1. 17.3% of the study population was excluded due to non-compliance.
2. Per-protocol analysis was used, leading to a reduced sample size, which may have affected the incidence of CTEPH.

5. Conclusions

The combination of echocardiography, V/Q scan and CTPAG can be used as a reasonable tool for early recognition & treatment of patients with persistent pulmonary hypertension and CTEPH, leading to significant reductions in morbidity & mortality.

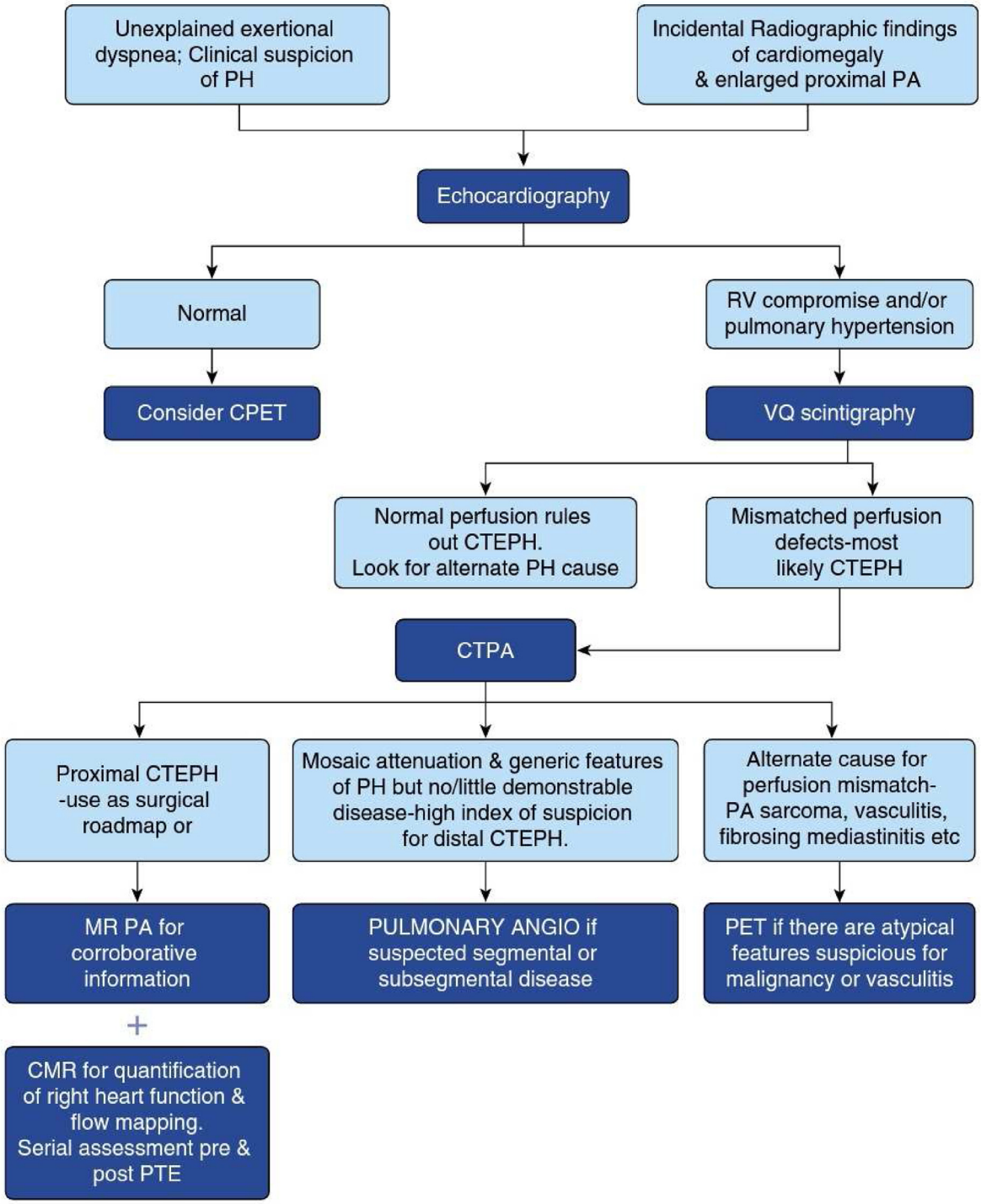

Fig. 1. Suggested diagnostic algorithm for the evaluation of patients with suspected chronic thromboembolic disease. CMR = cardiovascular magnetic resonance, CPET = cardiopulmonary exercise testing, CTEPH = chronic thromboembolic pulmonary hypertension, CTPA = computed tomographic pulmonary angiography, MR PA = magnetic resonance pulmonary angiography, PA = pulmonary artery, PET = positron emission tomography, PH = pulmonary hypertension, PTE = pulmonary thromboendarterectomy, RV = right ventricle, VQ = ventilation–perfusion.

Key message

Regular echocardiography on follow-up can help identify patients with PH and CTEPH early.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

There is no relationship with any industry. There is no conflict of interest.

Acknowledgements

We wish to acknowledge the support extended by the Research and Ethical Committee of SJICSR. We would also like to thank our radiology team for interpreting and reporting all the cases efficiently. We would also want to thank all the patients who gave consent & willingly participated in the study.

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