INTRODUCTION

Chronic thrombo-embolic pulmonary hypertension (CTEPH) is a life-threatening condition, wherein organised thrombi obstruct the pulmonary vascular bed causing a progressive increase in pulmonary artery systolic pressure (greater than 25mmHg) persisting for at least six months after the inciting event of acute pulmonary thrombo-embolism (PTE).\(^1\)\(^{-}\)\(^3\) There is limited information on the incidence and prevalence of CTEPH. The incidence of CTEPH is around 0.1% to 0.5% in patients surviving an acute PTE.\(^4\)\(^-\)\(^5\) The cumulative incidence following an acute PTE varies from 0.8% after four years\(^6\) or 3.8% after two years.\(^7\)

Although the understanding of the natural history of acute PTE and its evolution to CTEPH, and pathophysiology of CTEPH have greatly improved, the true frequency of CTEPH is likely under-estimated. There is a paucity of data about the incidence and prevalence of CTEPH from the Indian sub-continent. We investigated the clinical profile of acute PTE and the incidence of CTEPH over a one-and-a-half-year follow-up in a tertiary care cardiology hospital in Southern India.

MATERIAL AND METHODS

This observational study was carried out from January 2009 to June 2012. There was a total of 200 patients who were suspected to have acute PTE. The suspicion was based on the clinical scenario and the Wells pre-test probability scoring system. The clinical signs and symptoms raising the clinical suspicion were acute onset dyspnoea, orthopnoea, chest pain, haemoptysis and a loud second heart sound.

The diagnosis of acute PTE was confirmed in 104 patients by computed tomography pulmonary angiography (CTPA). After confirming the diagnosis, the patients were advised anticoagulation therapy with regular follow up and with monitoring of prothrombin time/international normalised ratio (PT/INR).

The patients were followed up every three months for one-and-a-half years. The 2D-eahocardiography was done on admission and then every three months. The CTPA was repeated at three months, six months and at one year of follow-up.

The diagnostic criteria used for CTEPH included symptoms of pulmonary hypertension, mean pulmonary artery systolic pressure (greater than...
25mmHg) on treatment with anticoagulation for a minimum of three months, with organised thrombus in the main pulmonary artery, lobar, segmental or subsegmental arteries.

### RESULTS

Out of the total 200 patients screened for suspected PTE, 104 were confirmed. Twelve patients dropped out and 92 completed the follow-up. The largest number of patients (41%) belonged to the age group of 41 to 60 years, while 30% were in the age group of 24 to 40 years and the remaining being 60+ years of age.

The most common symptom was dyspnoea followed by cough. Loud P2 followed by calf tenderness was the commonest sign. The clinical manifestations are shown in the figure. A multi-detector CT showed occlusion of the main pulmonary trunk in 20% of cases, the right pulmonary artery in 26% cases, the left pulmonary artery in 14% cases, and segmental pulmonary arteries in 40% of patients.

The predominant thrombophilic state in our study population was a combined deficiency of protein C and protein S in 30% of the cases, followed by antiphospholipid antibodies positivity in 28% patients, cancer in 18% cases, whereas 13% of patients had systemic lupus erythromatosis, with lupus antibodies positive, and homocysteine levels were high in 10% of the patients.

On follow up, 71% of the patients made an uneventful recovery in the one-and-a-half years follow-up. Twenty percent of the patients had developed CTEPH, after the first event of acute PTE during the follow-up. On a detailed analysis of this group of patients, it was found that they had a poor compliance on their long-term, oral anti-coagulation treatment; either they did not take the medication, or did not monitor the prothrombin time or international normalised ratio (INR) at regular intervals. All of them had their prothrombin time or INR in the sub-therapeutic level. Eigh percent of the patients died, while one percent had bleeding complications.

Low sodium levels (<130 meq/L), raised troponin, high brain-type natriuretic peptide (BNP) levels, increased right ventricular diameter on echocardiography, increased pulmonary artery diameter on multi-detector CT emerged as risk factors for an unfavourable outcome, i.e. CTEPH, bleeding episode and death.

### DISCUSSION

In acute PTE there is a mechanical obstruction of the pulmonary arteries at various levels, such as the main pulmonary artery, lobar vessels and segmental arteries, leading to increased vascular resistance, right ventricular dilatation, hypertrophy and right ventricular dysfunction with decreased right ventricular output. There is a ventricular septal coving towards the left, causing left ventricular cardiac output to decrease, resulting in hypotension. The embolus gets resolved either spontaneously or after interventions with thrombolysis, anti-coagulation, or surgery. In some cases, the thrombus can get organised and lead to CTEPH.

The primary site of initiation a thrombo-embolic event that eventually contributes to the development of CTEPH has been a subject of debate. There is compelling evidence supporting the concept that pulmonary embolism (PE) either overt or occult triggers a cascade of events that eventually result in CTEPH. Incomplete resolution and organisation of the thrombus, infection, inflammation with genetic predisposition and in-situ thrombosis can lead to vascular occlusion and stenosis. Simultaneously, the sheer stress in non-obstructed vessels and vascular remodelling causes increased pulmonary vascular resistance and pulmonary artery pressures causing CTEPH. This progression to pulmonary hypertension after the initiating event may be attributed to misguided pulmonary vascular remodelling in the entire pulmonary vasculature including both major and small vessels.

Risk factors for the development of CTEPH include malignancies, chronic inflammatory disorders, combined coagulation defects and anti-phospholipid antibody syndrome. Idiopathic PE, young age, large perfusion defect and recurrent embolism are associated with increased propensity to CTEPH according to the literature. Nevertheless, there are instances where CTEPH has occurred even in the absence of any prior PTE. In these scenario, the disease starts most likely by a thrombotic or inflammatory trigger in the pulmonary vasculature.

Previous studies from the Asian continent perceived venous thrombo-embolic events like deep vein thrombosis (DVT) to be a rare clinical entity.
In contrast, our study cohort revealed, 52% of patients who were screened had an acute PE and 20% of patients progressed to have a CTEPH in one-and-a-half-years time. This is in accordance with the more recent studies by Parakh et al from this part of the subcontinent, where out of 1552 consecutive patients with clinically suspected lower limb DVT, 70% patients had supra-popliteal DVT, and overall 47% of patients with a high-probability scan had no clinical manifestations suggestive of PE.

In our study, the rate of progression to CTEPH was surprisingly higher (20%) than that reported in the Western literature. The survivors of acute PE who progressed to CTEPH often failed to maintain follow-up, were poorly adherent to anti-coagulant medication and to regular monitoring of prothrombin time and international normalised ratio (PT-INR). The INR values of this subset of patients were below the target range. Further analysis of these patients revealed that raised BNP, troponins and low sodium were markers of adverse outcome. This observation is consistent with the previous studies also.

There are certain limitations of this study. There was a selection bias. Our study population was from a single tertiary care referral centre, with referrals from around the country for pulmonary endarterectomy for CTEPH. This might not be the true reflection of the general population. The follow-up period was quite short. Long-term follow-up is necessary to determine the natural course of this disease process.

CONCLUSIONS

Acute pulmonary embolism is an under-recognised but likely common clinical problem in India. A high index of clinical suspicion is necessary to diagnose it and confirm on computed tomographic pulmonary angiography. Increased availability of multi-detector computed tomography is likely to improve the diagnostic yield. Deficiency of protein C and protein S, the anti-phospholipid antibodies syndrome and malignancies account for the majority of acute pulmonary embolic events in India. A significant proportion of patients with acute PE may progress to CTEPH even within one year after the index event. Inadequate anticoagulation in patients with acute PTE predisposes to development of CTEPH. Early recognition, aggressive appropriate treatment and systematic follow-up can improve the outcome of this potentially fatal condition.

REFERENCES