respiratory MEDICINE

Impaired 6-min walk test, heart rate recovery and cardiac function post pulmonary embolism in long-term survivors

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Vincent Chow [a,b], Austin C.C. Ng [b], Leigh Seccombe [c],
Tommy Chung [b], Liza Thomas [d], David S. Celermajer [e],
Matthew Peters [c], Leonard Kritharides [a,b,*]

[a] ANZAC Research Institute, Sydney, Australia
[b] Department of Cardiology, Concord Repatriation General Hospital and The University of Sydney, Sydney, Australia
[c] Department of Thoracic Medicine, Concord Repatriation General Hospital and The University of Sydney, Australia
[d] Department of Cardiology, Liverpool Hospital and University of New South Wales, Australia
[e] Department of Cardiology, Royal Prince Alfred Hospital and The University of Sydney, Australia

Summary

Background: The functional capacity of long-term survivors of submassive pulmonary embolism (PE) is unreported. A six-minute walk distance (6MWD) <350 m and reduced heart rate recovery (HRR) indicate adverse prognosis in various chronic diseases.

Methods: Long-term survivors of acute PE (January 2000—June 2005) were invited to undergo prospectively planned six-minute walk test (6MWT), transthoracic echocardiogram (TTE), clinical and biochemical evaluation with cardiac biomarkers. HRR was calculated as the difference between heart rate at 6-min during and at 1-min post 6MWT.

Results: 120 patients (52 males; mean age [±standard deviation] — 65 ± 14 years) were identified 7.7 ± 1.4 years after PE. 6MWD was significantly lower than that predicted after adjustment for age, sex, and height (448 ± 114 m vs 475 ± 89 m, $p = 0.005$), and 16% (17/104) had 6MWD <350 m. Among patients with no baseline comorbidities at follow-up (Charlson comorbidity index = 0), 8% (4/52) had 6MWD <350 m. Resting TTE identified 29% of patients had raised right ventricular (RV) pulmonary pressure (pulmonary arterial systolic pressure [PASP] >36 mmHg) and 13% had impaired RV function. Patients with 6MWD <85% predicted had significantly greater impairment of RV longitudinal function ($p < 0.001$), higher PASP ($p < 0.001$) and pulmonary vascular resistance ($p < 0.001$), elevated NT-proBNP ($p = 0.03$) and high-sensitivity

* Corresponding author. Department of Cardiology, Concord Repatriation General Hospital and the University of Sydney, Hospital Road, Concord, NSW 2139, Australia. Tel.: +61 2 9767 7359; fax: +61 2 9767 6994.
E-mail address: leonard.kritharides@sydney.edu.au (L.Kritharides).

troponin-T (HsTropT, $p = 0.03$), but similar left ventricular systolic and diastolic function, to those with normal 6MWT.

Conclusions: Apparently well, long-term survivors of PE demonstrate impaired exercise capacity, heart rate recovery, mild pulmonary hypertension, raised PVR and right ventricular dysfunction associated with elevated NT-proBNP and HsTropT.

Introduction

Acute pulmonary embolism (PE) is common and associated with an early case fatality rate of 7−11%, with a reported 5-year cumulative mortality rate of up to 32% [1]. Recent studies identified characteristics of patients with a more guarded long-term prognosis after PE [2]. Although abnormal functional status has been reported in up to 41% of patients at six months after an acute PE [3], relatively little is known as to whether the long-term functional impairment is present in survivors.

The six-minute walk test (6MWT) and heart rate recovery (HRR) are practical and simple clinical tests that evaluate the integrated exercise responses of the pulmonary and cardiovascular systems, blood, neuromuscular units and muscle metabolism amongst patients of different age groups [4,5]. In a systematic review of various functional walk tests used in cardiorespiratory assessments, the 6MWT was shown to be easier to administer, better tolerated and more reflective of activities of daily living than other walk tests [6], and was easily incorporated into clinical practice. HRR after exercise assesses the changes in autonomic tone that occur immediately after cessation of exercise and reduced HRR has been shown to be a strong predictor of long-term adverse cardiac outcomes in healthy people [7] and in patients with pulmonary hypertension [8].

The present study examined the functional status of long-term survivors of acute PE using the 6MWT, HRR and echocardiography. Our primary hypothesis was that apparently well, long-term survivors of PE might demonstrate impaired functional capacity. If observed, a secondary aim of the study was to determine if the functional impairment was independent of patients' comorbidities, and/or related to subclinical right ventricular (RV) dysfunction or pulmonary hypertension.

Methods

Study population

Consecutive patients ($n = 1023$) admitted with a principal diagnosis of acute PE between January 2000 and June 2005 were identified retrospectively from a tertiary institution (Concord Hospital, Sydney, Australia) as previously reported [1,9]. Confirmed PE was defined according to published guidelines and required both documented clinical diagnosis and/or treatment of acute PE with therapeutic anticoagulation by the attending physician and an imaging study confirming the diagnosis of acute PE [10].

Important comorbidities during index PE admission, based on the International Classification of Disease, Tenth Revision, were recorded for each patient. The overall co-morbid status and short-term mortality risk of each patient were assessed and given a Charlson Comorbidity Index (CCI) score [11] and a simplified Pulmonary Embolus Severity Index (PESI) score respectively [12]. A CCI score ≥ 3 is associated with high mortality risk and independently predicts long-term outcome following acute PE [13]. Patients with a simplified PESI score ≥ 1 are classified as high risk and have a 30-day mortality of 10.9% [12].

Study protocol

The outcome status of all patients was first ascertained from the state death registry (New South Wales, Australia) with 100% complete follow-up. All patients who survived until 1st January 2010 ($n = 466$ patients, at least four years after the index PE) were invited by letter to prospectively participate in the study. Patients were subsequently contacted by telephone to arrange follow-up appointments. The exclusion criteria were: 1) patients declined to participate; 2) patients had dementia; 3) patients had relocated interstate or overseas; 4) did not consent to blood collection to be taken at time of review; or 5) were physically too infirm or otherwise incapable of attending for follow up review.

Patients who agreed to participate underwent the following assessments: 1) clinical review and examination; 2) electrocardiography to assess baseline heart rate and underlying cardiac rhythm; 3) spirometry to assess ventilatory function and exclude obstructive or restrictive lung disease; 4) echocardiography; 5) 6MWT to assess functional capacity; 6) blood tests including fasting lipid and glucose, and cardiac biomarkers [high-sensitivity troponin-T (HsTropT), high-sensitivity C-reactive protein (HsCRP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP)].

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by the institutional Human Research Ethics Committee, with written informed consent obtained from each patient.

Ventilatory function, six minute walk test and heart rate recovery

Spirometry was measured according to published criteria [14]. The presence of any underlying obstructive lung disease was classified according to the GOLD criteria [15]. The