Received: July 01 2014 | Accepted after revision: Nov 25 2014 | First published online: Jan 22 2015

Statement of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

Support statement: This study was supported by Investigator Initiated Research funding from Pfizer Inc. and in part by the Intramural Research Programme (National Institute of Allergy and Infectious Diseases (NIAID)). Funding information for this article has been deposited with FundRef.

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Eur Respir J 2015; 45: 1177–1179 | DOI: 10.1183/09031936.00169114 | 

# Serious adverse events during a 6-min walk test in patients with pulmonary hypertension

*To the Editor:*

The 6-min walk test (6MWT) is well standardised and, as per current guidelines, is deemed safe to perform in a range of patients [1]. In pulmonary arterial hypertension (PAH), 6-min walk distance (6MWD) is an important predictor of mortality and morbidity [2]. Moreover, changes in the 6MWD have been the primary end-point of most pivotal randomised controlled trials that have assessed the clinical response to specific pharmacological therapies in PAH [2].

To date there have been no published reports about the serious adverse events associated with the 6MWT, *e.g.* death, life-threatening events, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant incapacity, and substantial disruption to the ability to conduct normal life [3]. Perhaps the best reported study that supports the safety of the 6MWT is that of Enright *et al.* [4], which was performed in over 2000 elderly subjects (77±4 years of age) with a range of comorbidities. The authors reported no serious adverse events during the 6MWT, and whilst some participants stopped the test with chest pain, no emergency evaluation or therapy was required. More recently, in a review of 741 stable lung disease patients,

TABLE 1 Results from the most recent 6-min walk test (6MWT), echocardiograph and right heart catheterisation (RHC) for three adverse event cases

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| **6MWT** | | | |
| When completed | 3 months prior | 3 months prior | 5 months prior |
| 6-min walk distance m | 393 | 570 | 645 |
| Use of oxygen | Yes (2 L·min$^{-1}$) | No | No |
| End exercise $S_{pO_2}$ % | 76 | 79 | 90 |
| End exercise HR beats·min$^{-1}$ | 129 | 127 | 155 |
| End exercise dyspnoea (0–10) | 4 | 2 | 5 |
| Rests n | 0 | 0 | 0 |
| **Echocardiography** | | | |
| When completed | 3 months prior | 3 months prior | 6 months prior |
| LVEF % | 45 | 41 | 52 |
| RA area cm$^2$ | 30 | 31 | 33 |
| LA area cm$^2$ | 19 | 15 | 26 |
| RVSP mmHg | 95 | 72 | 100 |
| TAPSE mm | | 10 | 12 |
| RV dilatation | Severe | Severe | Severe |
| RV dysfunction | Severe | Severe | Severe |
| **RHC** | | | |
| When completed | 3 months prior | 3 months prior | 6 months prior |
| mPAP mmHg | 45 | 41 | 37 |
| mPVR Wood units | 7.0 | 12.7 | 7.6 |
| mRAP mmHg | 9 | 14 | 4 |
| TPG mmHg | 30 | 28 | 29 |
| PCWP mmHg | 15 | 10 | 8 |
| Cardiac index L·min$^{-1}$·m$^{-2}$ | 2.0 | 2.0 | 2.0 |
| Cardiac output L·min$^{-1}$ | 4.3 | 3.43 | 3.8 |

Tricuspid annular plane systolic (TAPSE) is not reported for case study 1. $S_{pO_2}$: arterial oxygen saturation measured by pulse oximetry; HR: heart rate; LVEF: left ventricular ejection fraction; RA: right atrium; LA: left atrium; RVSP: right ventricular systolic pressure; mPAP: mean pulmonary artery pressure; mPVR: mean pulmonary vascular resistance; mRAP: mean pulmonary right atrial pressure; TPG: transpulmonary gradient; PCWP: pulmonary capillary wedge pressure.

only 43 (6%) had an adverse event during or immediately after the 6MWT [5]. Notably none of these adverse events would have been classified as serious, with the majority (n=35) being instances in which the test was stopped because patient arterial oxygen saturation measured by pulse oximetry ($S_{pO_2}$) dropped below 80%.

Here we report three separate cases of serious adverse events (including one death) during or immediately after 6MWT in which pulmonary hypertension (PH) patients lost consciousness and required emergency attendance. All tests were conducted in a tertiary PH unit located at a large specialist thoracic hospital in Australia where 15–25 6MWTs are performed each week. In Australia, the 6MWT is routine practice as a requirement for an ongoing pharmaceutical benefit scheme. As per unit policy, the attending physiotherapist walks with the patient and monitors symptoms, heart rate (HR) and $S_{pO_2}$ every minute during the test. Criteria for stopping the test were excessive dyspnoea, diaphoresis, pallor, chest pain, leg pain, dizziness or light-headedness, and an HR <50–>170 beats·min$^{-1}$ [1]. Note that the unit does not apply a minimal $S_{pO_2}$ for stopping the test as many PH patients (*e.g.* those with congenital heart disease) tend to desaturate substantially during the test without accompanying adverse symptoms. Oxygen therapy is administered if resting $S_{pO_2}$ is <90% or if the patient is on long-term $O_2$ therapy. Results from the most recent 6MWT, echocardiograph and right heart catheterisation are presented in table 1 for each case study.

Case 1 was a 75-year-old male (New York Heart Association (NYHA) class III) with idiopathic pulmonary fibrosis and severe PH diagnosed 20 months prior to the event [6]. The patient underwent coronary angiography 1 month prior to the event, and mild coronary artery disease (CAD) (40% mid-right coronary artery) was demonstrated. Prescribed PH therapy was ambrisentan, in addition to aspirin, atorvastatin, telsimartan and prazosin. Medication had not changed and the patient had not reported any adverse events since the previous visit. The patient was reviewed by his physician ~1 h prior to the 6MWT, at which time blood pressure was 130/80 mmHg, resting HR was 88 beats·min$^{-1}$ and regular, jugular venous pressure was normal, and resting $S_{pO_2}$ (room air) 89%.

Medical records note that the patient completed 300 m at 5 min into the walk test and that initial $S_{pO_2}$ was stable, declining to 78%. At this point the patient reported dizziness and collapsed. Code was called and CPR commenced; however, ECG rhythm was asystole throughout the 30-min resuscitation period despite intravenous adrenalin, atropine, transcutaneous pacing, intubation and ventilation, and continuous CPR. It was not possible to resuscitate the patient and autopsy was declined.

Case 2 was a 25-year-old female (NYHA class II) with surgically repaired congenital heart disease-associated PH (common atrium repair at 6 months of age). A permanent pacemaker for sick sinus syndrome/atrial fibrillation was inserted at 6 years of age. The patient was on combination therapy consisting of bosentan, sildenafil and inhaled iloprost. Medication and patient status since the previous 6MWT were unchanged with no adverse events (including syncope) reported during this period.

The patient underwent routine 6MWT. 1 min post-6MWT the patient collapsed without warning. Immediately after 6MWT the patient had been talking coherently with the physiotherapist and had not reported any light-headedness. CPR commenced and ECG confirmed ventricular fibrillation; the patient and was successfully resuscitated following two direct current shocks. The patient was transferred to the intensive care unit, was confused and was self-ventilating on 8 $L \cdot min^{-1}$ $O_2$. Interrogation of the patient's pacemaker post arrest was suggestive of polymorphic ventricular tachycardia secondary to left ventricular dysfunction as a possible cause. Echocardiogram post arrest confirmed severe right ventricular (RV) dysfunction. Coronary angiogram and intravascular ultrasound (IVUS) with exercise excluded CAD and compression of the left main coronary artery (LMCA) from a dilated main pulmonary artery.

Case 3 was a 30-year-old male (NYHA Class II) with inoperable chronic thromboembolic PH who was prescribed combination therapy consisting of bosentan and sildenafil. Patient medication and disease severity had not changed since the previous 6MWT and no serious adverse events had been reported since the previous clinical visit.

The patient had completed 240 m of the 6MWT when he suddenly collapsed, lost consciousness and hit his head on the wall. The physiotherapist recorded and reported no warning symptoms of syncope. Code was called and the patient was self-ventilating $S_{pO_2}$ 90% at 10 $L \cdot min^{-1}$ $O_2$. HR and breathing rates were 70 beats $\cdot min^{-1}$ and 20 breaths$\cdot min^{-1}$, respectively, and blood pressure was 130/80 mmHg. There was spontaneous recovery within 2–3 min of the syncopal event and the patient did not require resuscitation. The patient was admitted and monitored. Subsequent coronary angiogram and IVUS with exercise demonstrated atrio-ventricular block and reproduced syncopal symptoms, and exercise testing was ceased. CAD was excluded as was compression of the LMCA from a dilated main pulmonary artery.

This study is novel as it is the first time that significant adverse events such as death or a life-threatening adverse event requiring hospitalisation have been reported as the result of conducting a 6MWT in any patient. None of the case studies met the current absolute contraindications to undertake the 6MWT, *i.e.* there was no history of unstable angina or heart attack in the previous month [1].

Whilst other studies have reported adverse events with the 6MWT, none of these events would be classified as a serious adverse event [4, 5, 7]. Our findings suggest that PH patients may be more at risk of serious adverse events during routine exercise tests such as the 6MWT.

Only one of the case studies had a pre-existing cardiac arrhythmia; however, this was paced. Whilst the incidence of cardiac arrhythmia in PH is well documented, the incidence of ventricular fibrillation is quite low [8]. In their study of 132 PAH patients who required CPR, Hoeper *et al.* [9] reported that only 10 had ventricular fibrillation (8%), whereas 58 (45%) patients had bradycardia, suggesting that bradycardia (which is inappropriate to the clinical scenario) is also a poor prognostic sign [10]. No evidence of bradycardia prior to 6MWT was seen in our case studies.

Whilst our subjects desaturated during the exercise test, it is unclear whether this degree of hypoxia is related to their arrhythmia. In a group of 19 interstitial lung disease patients, Park *et al.* [11] reported that 11 patients desaturated to <80% during the 6MWT. This level of desaturation was less than that reported during 24-h monitoring of $S_{pO_2}$. Moreover, none of the patients had a significant arrhythmia during the 6MWT but they all exhibited arrhythmias during the day. These daily arrhythmias were unrelated to the hypoxic state of the patients.

Whilst current recommendations would appear to suggest that minimal clinical supervision is required for the 6MWT, our results add a note of caution for patients with diagnosed PH. In each of the cases, the patients demonstrated severe RV dysfunction (table 1). Unlike other chronic heart and lung disease patients, PH patients appear more unstable and may warrant additional screening prior to undertaking a 6MWT. It is worth nothing that during a retrospective audit of >1200 6MWTs in our clinic, we discovered a further two patients who had syncopal events during their 6MWT. Neither of these required

resuscitation. Each case reported having syncopal events in the 3 months prior to their 6MWT. As a result, our clinical practice for the performance of a 6MWT has been modified to include a pre-screening medical questionnaire for events such as syncope, chest infection and change of medication as examples of an absolute contraindication to the conduct of 6MWT.

In summary, we have reported three separate cases of serious adverse events during the 6MWT in patients with severe RV dysfunction secondary to PH. Given that this appears to be the first time serious adverse events of this nature have been reported, we would argue there should be additional caution when exercise testing of any form (including shuttle walk test and supervised cardiopulmonary exercise test) is undertaken in individuals with severe RV dysfunction associated with PH.

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**The first ever reported cases of serious adverse events during the 6MWT in patients with pulmonary hypertension** http://ow.ly/FdVp8

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Received: Aug 10 2014 | Accepted after revision: Nov 24 2014 | First published online: Jan 22 2015

Conflict of interest: None declared.

Acknowledgements: The authors would like to thank Associate Professor Anne Holland (La Trobe University, Melbourne, Australia) for her comments on this manuscript.

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