References

- 1 Adjemian J, Olivier KN, Seitz AE, *et al.* Prevalence of nontuberculous mycobacterial lung disease in US medicare beneficiaries. *Am J Respir Crit Care Med* 2012; 185: 881–886.
- 2 CDC. Reported tuberculosis in the United States, 2012. Atlanta, US Department of Health and Human Services, 2013.
- 3 Lee M, Lee J, Carroll MW, *et al.* Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; 367: 1508–1518.
- 4 Schechter GF, Scott C, True L, *et al.* Linezolid in the treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2010; 50: 49–55.
- 5 Migliori GB, Eker B, Richardson MD, *et al.* A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009; 34: 387–393.
- 6 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; 40: 1430–1442.
- 7 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Linezolid to treat extensively drug-resistant TB: retrospective data are confirmed by experimental evidence. *Eur Respir J* 2013; 42: 288–290.
- 8 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2012; 16: 447–454.
- 9 Vinh DC, Rubinstein E. Linezolid: a review of safety and tolerability. *J Infect* 2009; 59: Suppl. 1, S59–S74.
- 10 Bishop E, Melvani S, Howden BP, *et al.* Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. *Antimicrob Agents Chemother* 2006; 50: 1599–1602.
- 11 Koh WJ, Kang YR, Jeon K, *et al.* Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; 67: 1503–1507.
- 12 Rey-Jurado E, Tudo G, de la Bellacasa JP, *et al.* *In vitro* effect of three-drug combinations of antituberculous agents against multidrug-resistant mycobacterium tuberculosis isolates. *Int J Antimicrob Agents* 2013; 41: 278–280.
- 13 Guna R, Munoz C, Dominguez V, *et al.* *In vitro* activity of linezolid, clarithromycin and moxifloxacin against clinical isolates of mycobacterium kansasii. *J Antimicrob Chemother* 2005; 55: 950–953.
- 14 Wallace RJ Jr, Brown-Elliott BA, Ward SC, *et al.* Activities of linezolid against rapidly growing mycobacteria. *Antimicrob Agents Chemother* 2001; 45: 764–767.

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 SpO 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. SpO₂: 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 (SpO₂) 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 SpO₂ 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 SpO₂ 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 SpO₂ is <90% or if the patient is on long-term O₂ 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, telmisartan 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 SpO₂ (room air) 89%.

Medical records note that the patient completed 300 m at 5 min into the walk test and that initial SpO₂ 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·min⁻¹ O₂. 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 SpO₂ 90% at 10 L·min⁻¹ O₂. HR and breathing rates were 70 beats·min⁻¹ and 20 breaths·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 SpO₂. 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 noting 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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References

- 1 American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
- 2 Galiè N, Corris PA, Frost A, *et al*. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D60–D72.
- 3 USFDA. Code of Federal Regulations Title 21, Volume 5. Food and Drug Administration Department of Health and Human Services Subchapter D - Drugs for Human Use. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32> Date last updated: April 1, 2014. Date last accessed: July 3, 2014.
- 4 Enright PL, McBurnie MA, Bittner V, *et al*. The 6-min walk test: a quick measure of functional status in elderly adults. *Chest* 2003; 123: 387–398.
- 5 Jenkins S, Cecins N. Six-minute walk test: observed adverse events and oxygen desaturation in a large cohort of patients with chronic lung disease. *Intern Med J* 2011; 41: 416–422.
- 6 Simonneau G, Gatzoulis MA, Adatia I, *et al*. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D34–D41.
- 7 Ameri A. Six minute walk test in respiratory diseases: a university hospital experience. *Ann Thorac Med* 2006; 1: 16–19.
- 8 Hoeper MM, Bogaard HJ, Condliffe R, *et al*. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D42–D50.
- 9 Hoeper MM, Galiè N, Murali S, *et al*. Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2002; 165: 341–344.
- 10 Rajdev A, Garan H, Biviano A. Arrhythmias in pulmonary arterial hypertension. *Prog Cardiovasc Dis* 2012; 55: 180–186.
- 11 Park JH, Jegal Y, Shim TS, *et al*. Hypoxemia and arrhythmia during daily activities and six-minute walk test in fibrotic interstitial lung diseases. *J Korean Med Sci* 2011; 26: 372–378.

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