Exercise cardiac MRI-derived right ventriculo-arterial coupling ratio detects early right ventricular maladaptation in PAH

To the Editor:

Exercise intolerance and right ventricular (RV) dysfunction are cardinal features of pulmonary arterial hypertension (PAH). Despite the significantly elevated afterload, patients rarely experience symptoms at rest until the late stages of the disease. Recent data suggest that the ability of the right ventricle to adapt to increased afterload is an important determinant of exercise capacity and outcome in PAH [1]. RV ejection fraction (RVEF) has been demonstrated to predict outcome [2]. There is also growing evidence that a noninvasively derived right ventriculo-arterial coupling ratio (VACR) may provide important prognostic information [3]. However, it remains unclear to what extent RV contractility is impaired during exercise and which metric best describes ventricular functional adaptation to afterload in PAH. We aimed to evaluate and compare the effects of submaximal exercise on RV systolic function and VACR in PAH and healthy subjects using cardiac magnetic resonance (MRI). We also examined and compared VACR and cardiopulmonary exercise test (CPET) in estimating the severity of disease.

Nine clinically compensated subjects with severe PAH (eight females aged 45.7±12.3 years, mean pulmonary artery pressure 55.8±18.7 mmHg, body mass index 24.8±3.3 kg·m^{-2}, World Health Organization functional class 2.2±0.4 and no significant valvular diseases) and nine healthy nonsmoking controls with no history of cardiorespiratory disease (six females aged 40.7±9.4 years, body mass index 23.4±2.7 kg·m^{-2}) participated. Mean 6-min walking distance for PAH subjects was 614.6±48.9 m. All PAH subjects were on stable combination PAH-specific therapies consisting of prostanoids (n=4), phosphodiesterase-5 inhibitors (n=8) and endothelin receptor antagonists (n=9). This study was approved by the institution's Research Governance Office (HREC/14/QPCH/47).

Cardiac MRI was performed on a clinical 1.5-T MR scanner (MAGNETOM Aera; Siemens Healthcare, Erlangen, Germany). A prototype ultrafast cine MRI sequence with a compressed sensing reconstruction was used to enable 12-fold acceleration of image acquisition [4] and RV function was measured utilising modified short-axis summation of slab volume technique [5]. Ventricular contractile reserve was defined as (ventricular function stress–ventricular function rest)/ventricular function rest. The approach from Sanz *et al.* [6] was used to calculate VACR=stroke volume/end-systolic volume (ESV).

Prior to cardiac MRI examination, CPET was performed outside the MRI scanner at two submaximal workloads (Ex1: 25 W; Ex2: ∼60% maximal age-predicted heart rate) using a portable metabolic system (Metamax; Cortex BXB, Lepzig, Germany). Workload at Ex2 corresponded to 44.3±7.9 W in PAH and 51.4±9.0 W in controls (p=0.14). Cardiac MRI exercise protocol consisted of a 3-min period of cycling in a supine position on an electromagnetically braked MRI cycle ergometer (Lode, Groningen, the Netherlands) at the same submaximal workloads. A median of two breath-holds was required at each workload for full ventricular coverage in the short-axis orientation.

Comparisons of rest-to-exercise cardiac MRI data between PAH and control groups and differences in rest-to-exercise responses within each group were calculated using ANOVA and t-tests. $p_{interaction}$ represents the p-value for the effect of exercise in PAH subjects in comparison with controls.

Resting RV stroke volume and RVEF were significantly higher in controls (p<0.05 for both). During exercise, both PAH and controls showed a similar and significant increase in heart rate (PAH *versus* controls, rest: 67±6 *versus* 66±16 beats·min^{-1}, Ex1: 89±10 *versus* 84±21 beats·min^{-1}, Ex2: 106±16 *versus* 99±23 beats·min^{-1}; $p_{interaction}$=0.261) and cardiac index (PAH *versus* controls, rest: 2.7±0.6 *versus* 2.8±0.8 L·min^{-1}·m^{-2}, Ex1: 4.0±0.5 *versus* 4.1±1.4 L·min^{-1}·m^{-2}, Ex2: 4.7±0.7 *versus* 5.0±1.6 L·min^{-1}·m^{-2}; $p_{interaction}$=0.766). RV systolic function as measured by ejection fraction and ESV augmented significantly from rest to exercise in controls, but not in PAH (figure 1a and b). Change in RV end-diastolic volume (EDV) or stroke volume during exercise was not significantly different between PAH and controls (figure 1c and d). Using ejection fraction as the metric, RV contractile reserve from rest to Ex2 was significantly higher in controls (20±13% *versus* −1±16%; p=0.032) (figure 1e).

At rest, VACR was similar between PAH and controls (0.9±0.3 *versus* 1.2±0.3, respectively; p=0.075). However, during exercise VACR failed to increase in PAH, whereas a significant increase in VACR was

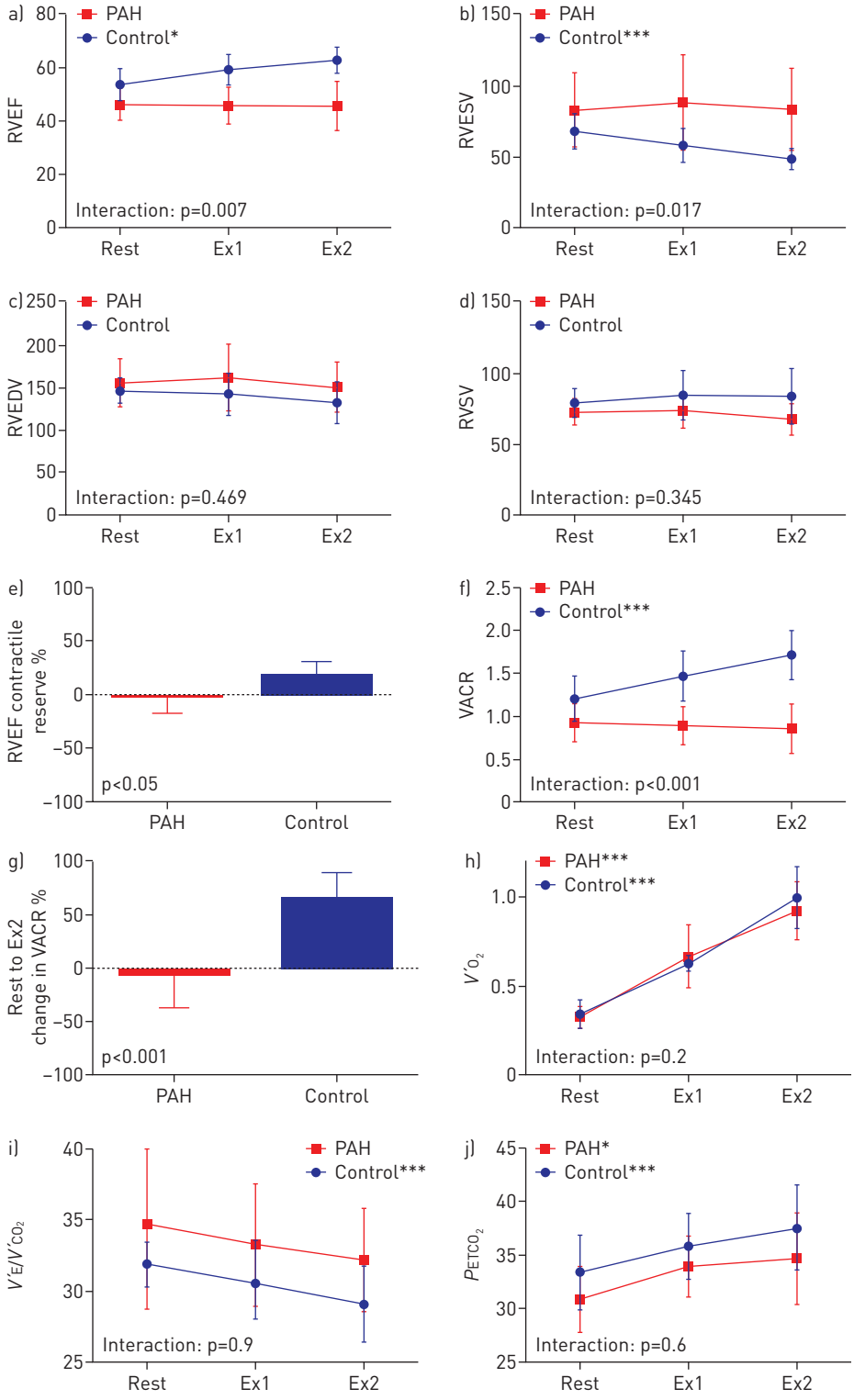

FIGURE 1 a) Right ventricular ejection fraction (RVEF) significantly increased in controls, but not in pulmonary arterial hypertension (PAH) subjects, implying an impaired exertional contractile reserve in PAH subjects. b) Right ventricular end-systolic volume (RVESV) decreased significantly in controls, but not in PAH subjects, implying an impaired systolic function in PAH subjects during exercise. c) Right ventricular end-diastolic volume (RVEDV) and d) right ventricular stroke volume (RVSV) did not change significantly in either group at the submaximal workloads achieved. e) RVEF contractile reserve measured from rest to Ex2 was significantly higher in controls compared with PAH subjects. f) Ventriculo-arterial coupling ratio (VACR) was maintained at rest but failed to augment during exercise in PAH subjects compared with controls. g) Change in VACR from rest to Ex2 was significantly greater in controls compared with PAH subjects. h) Oxygen uptake (V'_{O_2}) significantly increased in both groups during exercise with no significant difference between the groups. i) Ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}) decreased in both controls and PAH subjects during exercise. j) End-tidal carbon dioxide tension (P_{ETCO_2}) increased in both controls and PAH subjects during exercise. Ex1: exercise 1 (25 Watts); Ex2: exercise 2 (60% maximal age-predicted heart rate). Data are presented as mean±SD. *: p<0.05, significant change from rest to Ex1 and Ex2; ***: p<0.001, significant change from rest to Ex1 and Ex2.

observed in controls ($p_{interaction}<0.001$) (figure 1f). The change in VACR from rest to Ex2 was significantly higher in controls (66±15% *versus* −7±29%; p<0.001) (figure 1g).

No significant differences were found in resting oxygen uptake (V'_{O_2}), ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}) or end-tidal carbon dioxide tension (P_{ETCO_2}) between PAH and controls. During exercise, both PAH and controls showed a similar trend in V'_{O_2}, V'_E/V'_{CO_2} and P_{ETCO_2} with no significant difference between the groups ($p_{interaction}=0.2$, $p_{interaction}=0.9$ and $p_{interaction}=0.6$, respectively) (figure 1h–j).

We demonstrated that well-compensated, severe PAH subjects were unable to significantly increase RV pump function and VACR was inefficient during exercise compared with controls. In controls, augmentation of RVEF was due to a decrease in RVESV whilst RVEDV remained stable. In contrast, the PAH patients were not able to significantly augment RVESV to exercise. An RV that adapts well to chronically elevated pulmonary pressure is able to increase its contractility to match the increase in afterload, and loss of this capacity has been shown to be an early sign of RV dysfunction in PAH [7]. In controls, the lack of significant stroke volume change during exercise probably resulted from increased heart rate, reduced diastolic ventricular filling time and a decrease in EDV. Optimal ventriculo-arterial coupling, which allows for flow output at minimal energy cost, corresponds to a ratio of 1.5–2, with maximal ventricular efficiency reached at a ratio of 2 [8, 9]. VACR should be more load independent compared with ejection fraction [10] because ESV changes proportionally less than EDV at any given change in venous return. Despite the raised RV afterload in PAH patients, there was no significant difference in resting VACR between PAH and control subjects. This is consistent with recent studies showing relatively preserved VACR at rest in pulmonary hypertension patients [6, 11]. RVEF in control subjects increased by 20±13% from rest to Ex2, whereas VACR increased by 66±24%. The change in VACR was of a significantly higher magnitude compared to RVEF (p<0.001), suggesting that small changes may be more easily detected with this index and that stroke volume/ESV may potentially be better than ejection fraction for quantification of RV contractile reserve due to the inclusion of its variables. Nonetheless, determination of potential diagnostic and prognostic significance of this index will require further research.

Recent studies have shown that adding gas exchange analysis to the exercise test could help differentiate PAH patients from healthy control subjects and stratify their disease severities [12]. Ventilatory inefficiency in PAH is a distinct physiological abnormality characterised by an increase in V'_E/V'_{CO_2} and a lower P_{ETCO_2}, which are observed both at rest and during exercise. However, in our cohort of well-compensated, severe PAH patients with excellent 6-min walking distance we demonstrated that changes in V'_E/V'_{CO_2} and P_{ETCO_2} during exercise were insufficiently sensitive to differentiate PAH from control subjects.

We concluded that loss of dynamic changes in VACR assessed by exercise cardiac MRI may be a more sensitive index to identify severe PAH patients with early RV maladaptation.

@ERSpublications
In well-compensated PAH, early RV maladaptation is best captured by changes in SV/ESV at exercise by cardiac MRI http://ow.ly/MyEi302UUeL

Aaron C.W. Lin[1,2], Wendy E. Strugnell[1,2], Helen Seale[3], Benjamin Schmitt[4], Michaela Schmidt[5], Rachael O'Rourke[1,6], Richard E. Slaughter[1], Fiona Kermeen[7], Christian Hamilton-Craig[1,6] and Norman R. Morris[2]
[1]Richard Slaughter Centre of Excellence in Cardiovascular MRI, The Prince Charles Hospital, Brisbane, Australia. [2]Menzies Health Institute Queensland and Griffith University, Southport, Australia. [3]Physiotherapy Dept, The Prince Charles Hospital, Brisbane, Australia. [4]Siemens Healthcare Pty Ltd, Sydney, Australia. [5]Siemens Healthcare GmbH, Erlangen, Germany. [6]University of Queensland, Brisbane, Australia. [7]Pulmonary Hypertension Unit, The Prince Charles Hospital, Brisbane, Australia.

Correspondence: Aaron C.W. Lin, The Prince Charles Hospital, 627 Rode Rd Chermside, Brisbane, QLD 4032, Australia. E-mail: aaron.lin@health.qld.gov.au

Received: April 26 2016 | Accepted after revision: July 23 2016 | First published online: Sept 22 2016

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

References

1 Blumberg FC, Arzt M, Lange T, *et al.* Impact of right ventricular reserve on exercise capacity and survival in patients with pulmonary hypertension. *Eur J Heart Fail* 2013; 15: 771–775.
2 Zafrir N, Zingerman B, Solodky A, *et al.* Use of noninvasive tools in primary pulmonary hypertension to assess the correlation of right ventricular function with functional capacity and to predict outcome. *Int J Cardiovasc Imaging* 2007; 23: 209–215.
3 Vanderpool RR, Pinsky MR, Naeije R, *et al.* RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. *Heart* 2015; 101: 37–43.
4 Vincenti G, Monney P, Chaptinel J, *et al.* Compressed sensing single-breath-hold CMR for fast quantification of LV function, volumes, and mass. *JACC Cardiovasc Imaging* 2014; 7: 882–892.

5 Strugnell WE, Slaughter IR, Riley RA, *et al.* Modified RV short axis series – a new method for cardiac MRI measurement of right ventricular volumes. *J Cardiovasc Magn Reson* 2005; 7: 769–774.
6 Sanz J, Garcia-Alvarez A, Fernandez-Friera L, *et al.* Right ventriculo-arterial coupling in pulmonary hypertension: a magnetic resonance study. *Heart* 2012; 98: 238–243.
7 D'Alto M, Ghio S, D'Andrea A, *et al.* Inappropriate exercise-induced increase in pulmonary artery pressure in patients with systemic sclerosis. *Heart* 2011; 97: 112–117.
8 Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. *Circulation* 2009; 120: 992–1007.
9 Vonk-Noordegraaf A, Haddad F, Chin KM, *et al.* Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *J Am Coll Cardiol* 2013; 62: Suppl 25, D22–D33.
10 Sagawa K, Maughan L, Suga H, *et al.* Cardiac contraction and the pressure–volume relationship. New York, Oxford University Press, 1988.
11 Tedford RJ, Mudd JO, Girgis RE, *et al.* Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. *Circ Heart Fail* 2013; 6: 953–963.
12 Woods PR, Frantz RP, Taylor BJ, *et al.* The usefulness of submaximal exercise gas exchange to define pulmonary arterial hypertension. *J Heart Lung Transplant* 2011; 30: 1133–1142.

Eur Respir J 2016; 48: 1797–1800 | DOI: 10.1183/13993003.01145-2016 | Copyright ©ERS 2016

Shorter treatment for multidrug-resistant tuberculosis: the good, the bad and the ugly

To the Editor:

We welcome the initiative by the Guideline Development Group (GDG) members to issue the 2016 update of World Health Organization (WHO) treatment guidelines for drug-resistant tuberculosis (TB) [1]. With one in two patients currently failing on treatment for multidrug-resistant (MDR)-TB, primarily as a result of the difficulties presented by cumulative drug toxicity, logistics, costs and subsequent poor adherence to therapy [2], a shorter regimen for selected patients would be a tremendous asset, even though the GDG argues that the recommendation is conditional, and the scientific evidence for the recommendation is low. Since the first reports on the efficacy of a regimen of only 9 months for MDR-TB [3, 4], two more studies have been published to support the concept of shorter regimens [5, 6] while the STREAM (Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB) study is still enrolling [7]. However, shortening therapy would only apply for selected patients without prior use of or proven resistance to fluoroquinolones (group A) or second-line injectable agents (group B). At least five active drugs should be available for the intensive phase (4–6 months). Further exclusions are extrapulmonary TB, additional resistance to pyrazinamide (PZA) and pregnancy. Clofazimine [8] and linezolid [9] were regrouped as core agents in group C with ethionamide or prothionamide, while para-aminosalicylic acid was deferred to group D.

The GDG noted the lack of evidence for shortening treatment for extrapulmonary MDR-TB and did not recommend doing so, even though drug-susceptible extrapulmonary and pulmonary TB are treated with similar schedules and durations of treatment. MDR-TB treatment requires bacteriological monitoring, which is more feasible in sputum samples from pulmonary MDR-TB patients than samples from extrapulmonary MDR-TB cases.

Excluding PZA resistance is problematic. PZA susceptibility testing is difficult and not widely available, especially in low-resource settings. However, recent studies have shown excellent concordance of molecular and phenotypic susceptibility [10, 11], and testing molecular susceptibility to this important drug may become an important asset, even in low-resource settings.

We retrospectively analysed how many MDR-TB patients in the Netherlands would potentially have benefitted from the new guidelines; we therefore studied the data of all 172 consecutive patients that had started treatment since 2000. Data on patients treated between 2000 and 2009 have been published previously [8].

Five of these 172 patients had earlier MDR-TB treatment, four were pregnant, 30 had extrapulmonary MDR-TB, 28 had additional resistance to group A and/or group B drugs and 52 had PZA-resistant organisms. Four had extensively drug-resistant TB (these patients were included in our earlier report [8]), and all of these cases had a favourable outcome. As multiple exclusion criteria clustered in some patients