To the Editor:

We present a clinical case that highlights an important issue surrounding the limitations of normative reference values (NRV) for the interpretation of cardiopulmonary exercise testing (CPET). The patients gave written consent for their anonymised data to be presented. At present, for CPET there are many NRV available from different authors for both adult and paediatric populations [1–3]. Nevertheless, there is no single NRV available that encompasses both adult, paediatric and adolescent populations [1]. We highlight these issues in a paediatric subject and the urgent requirement for standardised age- and sex-related reference values for CPET, akin to the global lung initiative reference values for lung function [4].

CPET is utilised to assist with determining the underlying cause of exercise intolerance and/or symptoms of dyspnoea and fatigue, to assess the response to therapies and to better understand the risks associated with surgical interventions [2]. CPET results are interpreted using NRV to determine disease severity and cardiovascular fitness. As outlined previously, a number of NRV are available, but the majority of these studies from which the NRV are derived use small sample sizes, heterogeneous exercise protocols, variable normalisation strategies and inadequate adjustment for confounding variables [3]. The choice of NRV used impacts on the interpretation of CPET and clinical outcomes, as we demonstrate.

A 14-year-old girl was initially referred to Norfolk and Norwich University Hospital NHS Trust (NNUH) for investigation of exertional breathlessness and chest pain. Following an echocardiogram, computerised tomography pulmonary angiogram and magnetic resonance imaging (MRI), a subacute/chronic right main pulmonary artery thromboembolism was diagnosed with no apparent clear provoking factors. CPET results were consistent with a gas exchange defect with only a mild reduction in aerobic capacity (see table 1). Subsequently she was referred to the National Chronic Thromboembolic Pulmonary Hypertension multidisciplinary team meeting at Royal Papworth Hospital NHS Foundation Trust (RPH) where her case was reviewed and deemed technically suitable for pulmonary endarterectomy (PEA) surgery, but the risks of the operation outweighed the benefits. The decision was based on reduced thromboembolic load in a physically active patient with normal functional status for her age and no signs of pulmonary hypertension on noninvasive tests. Anticoagulation therapy was continued and followed up in her local hospital.

She was referred to the Pulmonary Vascular Disease Unit at RPH 6 months later, as she had become more breathless and was unable to continue with competitive ice skating. On review, several noninvasive tests were carried out and were within the normal range except for oxygen desaturation to 85% during a 6-min walk test (555 m achieved). The investigations included electrocardiogram, echocardiogram, blood results including full blood count, urea and electrolytes, liver function tests and N-terminal pro hormone B-type natriuretic peptide test. Pulmonary function tests demonstrated mild airway obstruction with normal gas transfer.

The decision to perform right heart catheterisation (RHC), the “gold standard” diagnostic tool for pulmonary hypertension [5], was deferred in this paediatric patient (who suffered with severe...
hospital-related anxiety) until after the CPET. CPET can detect characteristics consistent with pulmonary vascular disease [6], therefore offers valuable information for patient follow-up, assessment of treatment efficacy and prognosis.

A ramped incremental exercise test was performed on a cycle ergometer according to American Thoracic Society/American College of Chest Physicians (ATS/ACCP) guidelines [7] and results were interpreted using NRV from BONGERS et al. [8]. The results demonstrated a moderately reduced aerobic capacity with an anaerobic threshold consistent with a diseased status, evidence of desaturation and a mildly reduced oxygen pulse, which is often used as a surrogate for stroke volume (see table 1). Striking features on the nine-panel plots of the CPET were the raised ventilatory slope, raised ventilatory equivalents, reduced and persistent end-tidal carbon dioxide values and significant desaturation. All of these features point to a gas exchange abnormality.

Interestingly, these results were in contrast to those reported 1 year earlier during preliminary investigations at NNUH. These results suggested only a mild reduction in aerobic capacity with an anaerobic threshold suggestive of a deconditioned subject. The oxygen pulse was normal, but there was still evidence of desaturation. The nine-panel plots demonstrated very similar patterns to those identified on the RPH CPET. It was noted that NRV from COOPER et al. [9] were used to guide interpretation at NNUH, rather than BONGERS et al. [8], which we suggest underlies the significant difference in the reported results. More specifically, when comparing % predicted values for each test, it appeared that the patient’s functional status had significantly deteriorated (see table 1). However, further interrogation showed that absolute values of CPET parameters were comparable for each set of results, with the nine-panel plot demonstrating abnormal gas exchange for both. It was therefore apparent that the perceived change in functional status between CPETs was due to a difference in NRV applied, rather than as a consequence of a physiological deterioration. Further research is required to determine which set of NRV should be used to accurately characterise a patient’s true functional status or to risk stratify which surgical interventions and treatments are considered appropriate. In this case one could argue that the NRV from BONGERS et al. [8] were appropriate, given the identification of a gas exchange pattern on the CPET nine-panel plots with significant desaturation on both tests. This may, however, not be the case in all instances, and the lack of clarity with regards to the appropriate NRV to use leads to confusion and can be misleading.

Subsequently, the patient underwent RHC which demonstrated raised mean pulmonary arterial pressures (mPAP) (37 mmHg) and pulmonary vascular resistance (PVR) (497 dyn·s·cm$^{-5}$) with a reduced cardiac index (CI) (2.46 L·min$^{-1}$·m$^{-2}$). An MRI confirmed the diagnosis of chronic thromboembolic pulmonary hypertension and deterioration from World Health Organization Functional Class I (WHO FC) to WHO FC III. The patient’s risk and benefits for PEA surgery had changed, and she was offered surgical management, currently pending due to the coronavirus disease 2019 (COVID-19) pandemic.

### Table 1: Results for cardiopulmonary exercise testing (CPET) parameters with two different normative reference values (NRV) applied

| CPET variables | Norfolk and Norwich Hospital (Dec 2018) | Royal Papworth Hospital (Dec 2019) |
|----------------|----------------------------------------|-----------------------------------|
|                | Results (absolute) | Bongers 8–18 years (2014) % pred | Cooper 6–17 years (1984) % pred |
| Load W         | 89                      | 42%                                | 62%                                |
| $V_{O_2\text{peak}}$ mL·min | 1391                        | 55%                                | 70%                                |
| $V_{O_2\text{peak}}$ mL·min·kg | 23.5                        | 56%                                | 70%                                |
| $V_{O_2@AT}$ mL·min  | 879                                |                                    | 788                                |
| $O_2\text{pulse}$ mL | 8.9                             | 68%                                | 96%                                |
| $V'_E/V'_CO_2$ slope | 45                                | 52                                |
| $V'_EEqCO_2$ AT  | 44                              |                                    | 42                                |
| Lowest oxygen saturation % | 85                                |                                    | 88                                |
| Cardiovascular slope | Normal                        | Normal                            |
| AT % pred $V'_{O_2\text{max}}$ | 35%                            | 44%                                | 31%                                |
| $V'_O_2\text{peak}$ mL·min·kg | 23.5                        | 56%                                | 70%                                |
| $V'_E/V'_CO_2$ slope | 45                                | 52                                |
| $V'_EEqCO_2$ AT  | 44                              |                                    | 42                                |
| Lowest oxygen saturation % | 85                                |                                    | 88                                |
| Cardiovascular slope | Normal                        | Normal                            |
| AT % pred $V'_{O_2\text{max}}$ | 35%                            | 44%                                | 31%                                |

$V'_O_2\text{peak}$: peak oxygen consumption; $V_{O_2@AT}$: oxygen consumption at anaerobic capacity; $V'_EEqCO_2$ at AT: ventilatory equivalents for carbon dioxide at anaerobic threshold; AT % pred $V'_{O_2\text{max}}$: anaerobic capacity as a per cent of maximal predicted oxygen consumption. $V'_E/V'_CO_2$ slope: The slope of the relationship between ventilation and carbon dioxide production.
To determine whether our findings were consistent among a wider paediatric population, paediatric CPET results were analysed from tests performed between 2009 and 2019 (n=766; 56% male, 44% female; range 5–18 years) at the Royal Hospital for Children, Glasgow. Percentage of predicted values (% pred) for aerobic capacity (peak oxygen consumption, $V'_{O2\text{peak}}$) were generated using those NRV reported by Cooper et al. [9] and Bongers et al. [8]. Bland–Altman analysis demonstrated that applying the Cooper et al. NRV resulted in a $V'_{O2\text{peak}}$ % pred that was on average 11% greater than that observed when Bongers et al. NRV were used. It was also noted that limits of agreement were wide with −26 to 48% $V'_{O2\text{peak}}$ % pred between the two NRV. There are limitations of expressing results as % pred and not standardised residuals and lower limits of normal, which take into account the range of values found in the reference population whereas % pred do not [10]. Nevertheless Cooper et al. NRV did not provide relative standardised deviation; therefore, confidence limits could not be calculated for these NRV.

In summary this case and subsequent analysis has highlighted two important issues. First, CPET NRV are not standardised, and therefore this may lead to a significant difference in result interpretation between different medical institutions. Second, inadequate NRV have an impact on differential diagnosis, risk stratification and appropriateness for surgical and invasive intervention. There is an urgent requirement for CPET age-related reference values to be harmonised to ensure appropriate clinical interpretation and patient management.

Jessica L. Waterfall $^1$, Paul Burns $^2$, Dawn Shackell$^3$, Joanna Pepke-Zaba$^4$, Katrina E. Oates$^1$ and Karl P. Sylvester$^{1,5}$

$^1$Respiratory Physiology, Royal Papworth Hospital NHSFT, Cambridge, UK. $^2$Respiratory and Sleep Physiology Dept, Queen Elizabeth University Hospitals, Glasgow, UK. $^3$Respiratory Physiology, Norfolk and Norwich University Hospital NHSFT, Norwich, UK. $^4$Pulmonary Vascular Disease Unit, Royal Papworth Hospital NHSFT, Cambridge, UK. $^5$Lung Function Unit, Cambridge University Hospitals NHSFT, Cambridge, UK.

Correspondence: Karl P. Sylvester, Respiratory Physiology Dept, Royal Papworth Hospital NHS Foundation Trust, Papworth Road, Cambridge Biomedical Campus, Cambridge, CB2 0AY, UK. E-mail: karl.sylvester@nhs.net

Received: 1 June 2020 | Accepted after revision: 5 Oct 2020

Conflict of interest: J.L. Waterfall has nothing to disclose. P. Burns has nothing to disclose. D. Shackell has nothing to disclose. J. Pepke-Zaba has received speaker fees and honoraria for consultations from Actelion and Merck, and her institution has received educational grants from Actelion and Merck. K.E. Oates has nothing to disclose. K.P. Sylvester has nothing to disclose.

References

1. Takken T, Mylius CF, Paap D, et al. Reference values for cardiopulmonary exercise testing in healthy subjects – an updated systematic review. Expert Rev Cardiovasc Ther 2019; 17: 413–426.
2. Guazzi M, Arena R, Halle M, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Eur Heart J 2018; 39: 1144–1161.
3. Blais S, Berbari J, Counil FP, et al. A systematic review of reference values in pediatric cardiopulmonary exercise testing. Pediatr Cardiol 2015; 36: 1553–1564.
4. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir Soc 2012; 40: 1324–1343.
5. Galé N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Respir J 2015; 46: 903–975.
6. Held M, Kolb P, Grün M, et al. Functional characterization of patients with chronic thromboembolic disease. Respir Care 2016; 91: 503–509.
7. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211–277.
8. Bongers BC, Hulzebos HJ, Van Brussel M, et al. Pediatric Norms for Cardiopulmonary Exercise Testing: In Relation to Sex and Age. Uitgeverij BOXpress, 2014.
9. Cooper DM, Weller-Ravell D. Gas exchange response to exercise in children. Am Rev Respir Dis 1984; 129: 2 Pt. 2, S47–S48.
10. Miller M, Pincock A. Predicted values: how should we use them? Thorax 1988; 43: 265–267.