Letter to the Editor

Letter to the Editor: Validity and reliability concerns associated with cardiopulmonary exercise testing young people with cystic fibrosis. Response to: Statement on Exercise Testing in Cystic Fibrosis (Hebestreit *et al.*, 2015 *Respiration* 90(4):332-51)

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Short Title: Validity and reliability concerns associated with CPET in CF

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The recent statement by Hebestreit and colleagues [1] on behalf of the European Cystic Fibrosis Society (ECFS) Exercise Working Group and endorsed by the European Respiratory Society, should be commended for their efforts to establish consensus regarding exercise testing for young people with CF. Exercise testing is a valuable investigative tool for the the clinical management and scientific investigation of children and adolescents with CF and this document provides an international standpoint regarding the importance of cardiopulmonary exercise testing (CPET) within the management of this patient group. However, it is our view that the authors have missed an opportunity to provide a contemporary and comprehensive overview of the CPET 'toolkit' currently available.

The authors state that this document will *'describe the current best practice recommendations for conducting exercise tests in patients with CF'* and *'summarises the information available on specific test protocols and outcome parameters (Page 2)'.* The authors recommend the Godfrey protocol [2] when using the cycle ergometer, with measures of arterial oxygen saturation and, when possible, pulmonary gas exchange and ventilation. Whilst this does represent progress from the routinely used shuttle and step tests, the authors failed to acknowledge several limitations inherent to the Godfrey protocol and the recommended use of criteria to verify a maximal test. This is surprising, given that the ECFS Clinical Trials Network Standardisation Committee recently called for research assessing the validity, reproducibility and feasibility of outcome measures utilised in the assessment of patients with CF and the most appropriate exercise test for paediatric patients [3].

The authors rightfully acknowledge that an issue with shuttle and step tests is that it can be difficult to determine whether a maximal effort was made. However, they then state that *'the Godfrey protocol provides valid information for all CF relevant indications for an exercise test'*. The authors recommend that since not all individuals display the tradition verification criterion of a plateau in oxygen uptake ($\dot{V}O_2$) upon exhaustion, at least one of the following

should be used to confirm a maximal effort: the patient achieves a predicted $\dot{V}O_{2peak}$ or peak power output (W_{peak}); the patient reaches maximal heart rate (HR_{max}), peak ventilation approaches maximal voluntary ventilation, respiratory exchange ratio (RER) is > 1.03, exertion is 9-10 on the 0-10 scale or ≥17 on a 7-20 scale. However, our research group recently demonstrated that the use of secondary criteria to confirm a maximal effort (e.g. RER > 1.00 or 1.10, HR of 180 b·min^{-1} or 95% age-predicted HR_{max}), in line with those recommended by Hebestreit *et al.* [1], are invalid and can drastically underreport maximal $\dot{V}O_{2max}$ in some young people with CF [4], a finding consistent with healthy children and adolescents [5]. Accepting submaximal or rejecting 'true' maximal values can distort the clinical application and interpretation of CPET, which is important given that $\dot{V}O_{2max}$ is an indicator of prognosis [6,7], quality of life [8] and risk of hospitalisation for exacerbations [9] in people with CF.

Given the limited use of secondary verification criteria to verify a maximal CPET effort in young people with CF, we have developed an alternative protocol to do so. A procedure termed the 'supramaximal verification phase' (S_{max}), in which an exhaustive ramp incremental test precedes an exhaustive individualised constant work rate test at an intensity above W_{peak}, can confirm whether a 'true' measure of $\dot{V}O_{2max}$ has been obtained, which is fundamental to the utility of this outcome parameter in CF. Significantly, this finding is in line with data in healthy adults [10-18], children [5] and other paediatric clinical groups [19]. Although the authors present information regarding *'was the test maximal?',* they failed to reference this published evidence and presented inaccurate verification criteria as *best* CPET practice for young people with CF, which we feel should be approached with caution. This statement also provides a summary of the reliability of exercise tests for young people with CF, however again published evidence has been ignored. We recently reported both the short- and medium-term reproducibility of a valid CPET protocol for young people with CF [4],

which was shown to reduce the error of measurement when compared with an isolated incremental CPET to derived $\dot{V}O_{2peak}$ [20]. To the best of our knowledge we are not aware of any reproducibility or validity data for $\dot{V}O_{2max}$ in young people with CF derived using the Godfrey protocol.

Whilst the focus of this letter addresses validity and reproducibility issues with the Godfrey protocol, other important issues to consider are: 'step' increases in work rate derived exclusively from stature can result in insufficient test durations of ≤ 4 minutes [21]. This procedure limits our ability to characterise the progressive increase in $\dot{V}O_2$ during exercise and determine submaximal measures of aerobic fitness (e.g. the gas exchange threshold or $\dot{V}O_2$ mean response time) which, as highlighted in this consensus statement, may provide better predictors of mortality in adolescents with CF [22]. In accordance with others [23], we recommend a ramp incremental exercise test, which aims to reach volitional exhaustion in 8-12 minutes [24], followed by S_{max} verification of maximal CPET parameters. Not only has this testing protocol been demonstrated as safe and feasible in young people with CF in a research setting, it is also now used as part of patients' annual clinical review with UK based CF clinics in Exeter, Southampton and Portsmouth, demonstrating the feasibility of its clinical implementation. The CF-specific linear regression model to predict W_{peak} and calculate individualised workload increments to reach volitional exhaustion in ~ 10 minutes developed by Hulzebos and colleagues should help prevent short test durations [25].

Whilst it is recognised that there are no large scale studies directly comparing exercise testing protocols, we feel the authors could have provided a more contemporary overview of the evidence concerning the validity and reproducibility of CPET protocols available for use in young people with CF. If the clinical utility of CPET to provide a comprehensive evaluation

of physiological (dys)function and stratify patients with CF is to be realised, these important practical considerations must be acknowledged.

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