

1 **Cardiopulmonary exercise testing in young people with cystic fibrosis –**
2 **methods, limitations, and clinical practice**

3
4 **Dr Owen Tomlinson, Dr Alan Barker & Professor Craig Williams FBASES**
5 **Children’s Health and Exercise Research Centre, University of Exeter**

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7 Cystic fibrosis (CF) is a genetically inherited disease that currently affects ~11,000
8 people in the UK. The disease presents with an accumulation of thick mucus that
9 blocks the airways and digestive systems, and can reduce exercise tolerance and
10 increase breathlessness. As there is currently no cure for CF, exercise forms an
11 important treatment and regular exercise testing is recommended, with
12 cardiopulmonary exercise testing (CPET) acknowledged as the ‘gold standard’ by
13 international clinical organisations (Hebestreit et al., 2015). Aerobic fitness (as defined
14 using peak oxygen uptake, $\dot{V}O_{2peak}$), a primary outcome of CPET, is significantly
15 associated with mortality in CF (Vendrusculo et al., 2018), highlighting the need to
16 accurately identify this value and understand pathophysiological causes behind any
17 changes. However, there are several aspects surrounding its application that have
18 warranted further investigation.

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20 By its nature, maximal exercise testing requires maximal effort from patients, which is
21 not always possible due to clinical status, breathlessness or motivation. As such,
22 suitable submaximal parameters have warranted investigation. This programme of
23 research investigated the oxygen uptake efficiency slope; firstly utilising allometric
24 scaling to remove residual effects of body size (Tomlinson et al., 2017b), then
25 subsequently determining its invalidity as a submaximal alternative to $\dot{V}O_{2peak}$, as it is
26 unable to discriminate fitness in the same way as $\dot{V}O_{2peak}$ (Williams et al., 2018).
27 However, we identified that the oxygen uptake efficiency plateau instead holds
28 interesting potential, as it does not require scaling for body size, and is associated with
29 disease status and severity in CF (Tomlinson et al., 2018a). Interestingly, these results
30 contrast similar studies in heart failure, highlighting that clinical groups cannot be
31 simply grouped together, but that each warrants its own dedicated avenue of research.

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33 Furthermore, this programme of research has further utilised CPET, alongside
34 magnetic resonance imaging, to investigate the musculoskeletal basis of exercise

35 intolerance in CF. This research identified that once thigh muscle volume has been
36 fully quantified (not estimated) and mathematically scaled for, there remains a
37 difference in $\dot{V}O_{2peak}$ between children with CF, and healthy matched controls
38 (Tomlinson et al., 2017a). This therefore provides evidence towards a qualitative
39 defect in skeletal muscle in CF, which has implications for management of the disease,
40 in particular the selection of exercise training regimens to improve musculoskeletal
41 health.

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43 Finally, a clinical application of research findings is essential for the benefit of the end
44 user – people with CF themselves. Integrating CPET into standard clinical care is a
45 priority, and to fulfil this requirement, a working group of clinically-based exercise
46 professionals has been established in the UK. This 'Cystic Fibrosis and Exercise
47 Network' has an emphasis on continued professional development, meeting annually
48 to exchange best practice. Surveys from this group reveals that exercise technicians
49 (individuals typically trained in sport and exercise sciences) play an increasingly
50 important role in clinics, responsible for exercise testing and training within CF centres.
51 We have also been identified that one-third of clinical teams are not confident in
52 discussing exercise with patients (Tomlinson et al., 2018b), thus highlighting an urgent
53 need to improve, increase, and standardise exercise education for clinicians in both
54 CF and beyond.

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56 There is a promising future for applied exercise science in clinical environments, as
57 well as an anticipated need for increased numbers of exercise scientists in clinical
58 roles. As the importance of exercise in the management of CF continues to grow, as
59 does the demand on both health care professionals and the exercise science
60 community to collaborate and further integrate exercise into health care for chronic
61 disease.

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63 **Authors**

64 Owen is an Associate Research Fellow at the University of Exeter.

65 Alan is a Senior Lecturer in Paediatric Exercise and Health at the University of Exeter.

66 Craig is a Professor of Paediatric Exercise and Health and Director of the Children's
67 Health and Exercise Research Centre at the University of Exeter.

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