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Title: Cardiopulmonary Exercise Testing in Chronic Lung Diseases: summary of key findings from the ERS task force

Authors: Thomas Radtke¹, Ioannis Vogiatzis^{2,3*}, Don S Urquhart⁴, Pierantonio Laveneziana^{5,6}, Richard Casaburi⁷, Helge Hebestreit^{8*} ⁹on behalf of the European Respiratory Society Task Force on Standardisation of Cardiopulmonary Exercise Testing in Chronic Lung Diseases

Affiliations: ¹ Division of Occupational and Environmental Medicine, Epidemiology, Biostatistics and Prevention Institute, University of Zurich and University Hospital Zurich, Switzerland; ² First Department of Respiratory Medicine, National & Kapodistrian University of Athens, Greece; ³ Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria University Newcastle, United Kingdom; ⁴ Department of Paediatric Respiratory and Sleep Medicine, Royal Hospital for Sick Children, Edinburgh, United Kingdom; ⁵ Sorbonne Université, INSERM, UMRS1158 Neurophysiologie respiratoire Expérimentale et clinique, F-75005 Paris, France; ⁶ AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service des Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée du Département "R3S", F-75013, Paris, France; ⁷ Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA, ⁸ Paediatric Department, University Hospital Würzburg, Würzburg, Germany, ⁹ A full list of members of the Task Force can be found in the Acknowledgements section.

* Task Force Co-Chair

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Correspondence: Prof. Dr. Helge Hebestreit, Universitäts-Kinderklinik, Josef-Schneider-Str. 2
97080 Würzburg, Germany, E-mail: hebestreit@uni-wuerzburg.de

Cardiopulmonary exercise testing (CPET) is a powerful diagnostic and prognostic tool in the management of people with a variety of chronic lung diseases [1–5]. Despite the remarkable increase in the number of publications on CPET over the past decades [2], CPET remains underutilised in the field of respiratory medicine. Numerous challenges to increase the use of CPET in both clinical practice and research await resolution including the establishment of global reference values, in line with those available for lung function and pulmonary diffusing capacity [6, 7]. Prior to such an international effort, strict standardisation of testing procedures is indispensable to obtaining valid and reliable results and to enable interpretation of CPET results within and between centres and individuals. Furthermore, an internationally standardised protocol is a prerequisite for the use of CPET data in patient registries and in retrospective collaborative research.

Previous statements by the European Respiratory Society (ERS) [8–10] and the American Thoracic Society and the American College of Chest Physicians (ATS/ACCP) [11] partly address standardisation, but none of these statements included information on the standardisation of CPET procedures—with regard to a range of lung diseases, nor considered the patient’s experience of CPET. As a consequence, various protocol modifications are used across the world, which may impact the choice of reference data and interpretation. The aim of the current document was to provide a strict technical standardisation of CPET procedures that could be applied to multiple respiratory conditions.

A European Respiratory Society (ERS) Task Force of adult and paediatric physicians, physiologists, exercise scientists and methodologists with expertise in CPET across a wide range of lung diseases conducted a rigorous systematic literature review to provide a comprehensive account of published CPET procedures to be uniformly applied across different settings such as research and/or clinical practice. Importantly, to gather patients’ perspectives on CPET, we conducted an online survey supported by the European Lung Foundation (ELF).

The systematic literature review identified 7914 studies, of which 595 studies with 26,523 patients were included in the quantitative analysis [12]. Among included studies, the most common lung diseases were chronic obstructive lung disease (COPD) and emphysema (54%), cystic fibrosis (CF, 13%), pulmonary arterial hypertension (11%) and lung cancer (7%). Whenever the literature review could not inform the Task Force on specific questions, existing guidelines and technical standards were used [8–11].

“Cycle ergometry is the preferred testing modality across various lung diseases”

Cycle ergometry (92% of studies) compared to treadmill ergometry (8% of studies) was the preferred testing modality across a wide range of lung diseases (figure 1). Overall, the percentage of studies employing 1-minute work rate increments was higher compared to ramp protocols for cycle and treadmill exercise testing; see figure 1. While there was a clear preference for minute-by-minute cycle ergometer testing protocols in studies with COPD and CF patients, a protocol preference was less clear for other lung diseases. Reasons for protocol choices could not be systematically evaluated from the majority of original studies.

“Ramp or minute-by-minute protocols are best suited for CPET in chronic lung diseases”

As already recommended in previous statement and guidelines by the ERS and ATS/ACCP [8, 11], incremental exercise protocols with stages of up to 1 minute maximum are best to assess people with chronic lung diseases since such protocols not only allow the measurement of peak values but are preferred to evaluate important variables during submaximal exercise stages such as the ventilatory anaerobic threshold, the slope of the minute ventilation - carbon dioxide output relationship and the slope of oxygen uptake - work rate relationship. If stages are longer, the adjustments to the change in

work rate will be visible in the ventilatory and gas exchange data, thereby reducing the precision of determining the above CPET outcomes.

“Exercise protocol was further standardised”

In line with previous statements and guidelines, the systematic literature review [12] supports a test protocol with a resting phase lasting at least 3 minutes [8–11], a 3-minute “unloaded” phase at the lowest work rate provided by the cycle ergometer [8, 9, 11], and an 8- to 12-min incremental phase with equal work rate increments every minute [8], followed by a recovery phase of at least 2-3 minutes.

The Task Force also aimed to establish disease-specific work rate increments using an approach similar to that of Wasserman et al. [13]. However, work rate increments have proved difficult to estimate due to the lack of reported patient data sets and heterogeneity of lung diseases that clearly limits the use of the work rate increment estimations for clinical practice. Previous studies have provided work rate increment estimation for cycle ergometry for people with COPD [14], CF [15], asbestosis, silicosis and asthma [16] and for treadmill testing for healthy adults [17, 18] and COPD patients [19, 20]. Other, more general recommendations for the selection of work rate increments are based on estimated peak oxygen uptake (VO_{2peak}) and VO_2 during unloaded pedalling [8]. Based on the data available from the literature review, some additional guidance is given for the selection of minute-by-minute increments in work rate in the full technical standard document [12].

The rigorous systematic literature review identified a large heterogeneity and substantial lack of information with respect to the quality of reporting on CPET equipment, testing protocols and criteria to determine maximal effort in the original publications [12]. Based on a lack of sufficient information, the

Task Force made suggestions regarding the operational dataset to be reported in future studies in order to achieve standardisation of CPET in lung diseases.

Of studies reporting CPET protocol details for cycle ergometry, only about 42%, 58% and 10% provided information on the duration of the resting phase, unloaded phase and recovery phase, respectively. For treadmill ergometry, protocol information was given even less often (14%, 39% and 8%). The selection of workrate increments (*e.g.* minute-by-minute or continuous) for cycle and treadmill exercise testing was rarely reported in the original studies. About 8-10% of all included studies did not provide *any* information on the chosen work rate increment.

Interpretation of CPET results

In general, the interpretation of CPET results requires the integration of testing results with the patient's medical history, and other clinical findings and investigations. The results of an exercise test may prompt further clinical investigations (*e.g.* vascular assessment, assessment of respiratory or peripheral muscle function). In this context, feedback from the patient, including reason for exercise termination, can be useful in evaluating exercise limitation. The Task Force report [12] provides a description and algorithm of how Task Force members interpret CPET results.

“Patient survey participants perceive exercise testing as beneficial and suggest annual testing as optimal“

With support by the ELF, the Task Force conducted an online survey available in 34 languages to assess patients' perspectives to gain insights into their perceived relevance and burden of taking part in CPET-related investigations. Two hundred ninety-five patients from 34 countries responded to the survey. The majority were patients with COPD (26%), sarcoidosis (18%), CF (16%) or asthma (13%). Responders were asked about the benefits of taking part in CPET with 75% reporting improved knowledge about

lung function as the greatest benefit. Many patients perceived the CPET as a highly beneficial part of their check-up and provided suggestions that informed this ERS Task Force [12]. For example, responders wished to perform CPET in a quieter environment, having the opportunity to sip water or to use a fan during the recovery period. In addition, patients highlighted the need for more information about the testing procedures and improved individual care during the test. Such information is highly relevant and might be incorporated by people conducting and supervising CPETs in their daily work. When asked how much of a problem aspects of CPET were, responders rated as “serious problems”: dryness in mouth (11%), muscle soreness (10%), bicycle seat discomfort (9%), coughing (9%), and mouthpiece discomfort (8%).

The preferred frequency for participating in CPET reported by nearly 75% of respondents was at least yearly (figure 2).

Future research directions

The Task Force identified important gaps with respect to CPET protocol standardisation [12]. Future research should focus on the standardisation of work rate increments for different lung diseases and the collection of large CPET datasets to establish normal values for relevant CPET outcomes in healthy subjects across age, including sufficient female and male subjects and a wide range of ethnicities. Ideally this should occur in a collaborative effort between the ERS and the Global Lung Function Initiative (GLI) [6, 7]. Moreover, future work should address the measurement properties (*i.e.* test-retest reliability and responsiveness to change) of CPET using appropriate analytical methods in patients with various lung conditions and across a broad range of disease severity. Finally, this Task Force identified a clear lack of studies comparing different CPET procedures (*e.g.* cycling versus treadmill; different duration of warm-up periods; minute-by-minute versus ramp work rate increments; impact of inspiratory capacity manoeuvre frequency) on exercise testing results.

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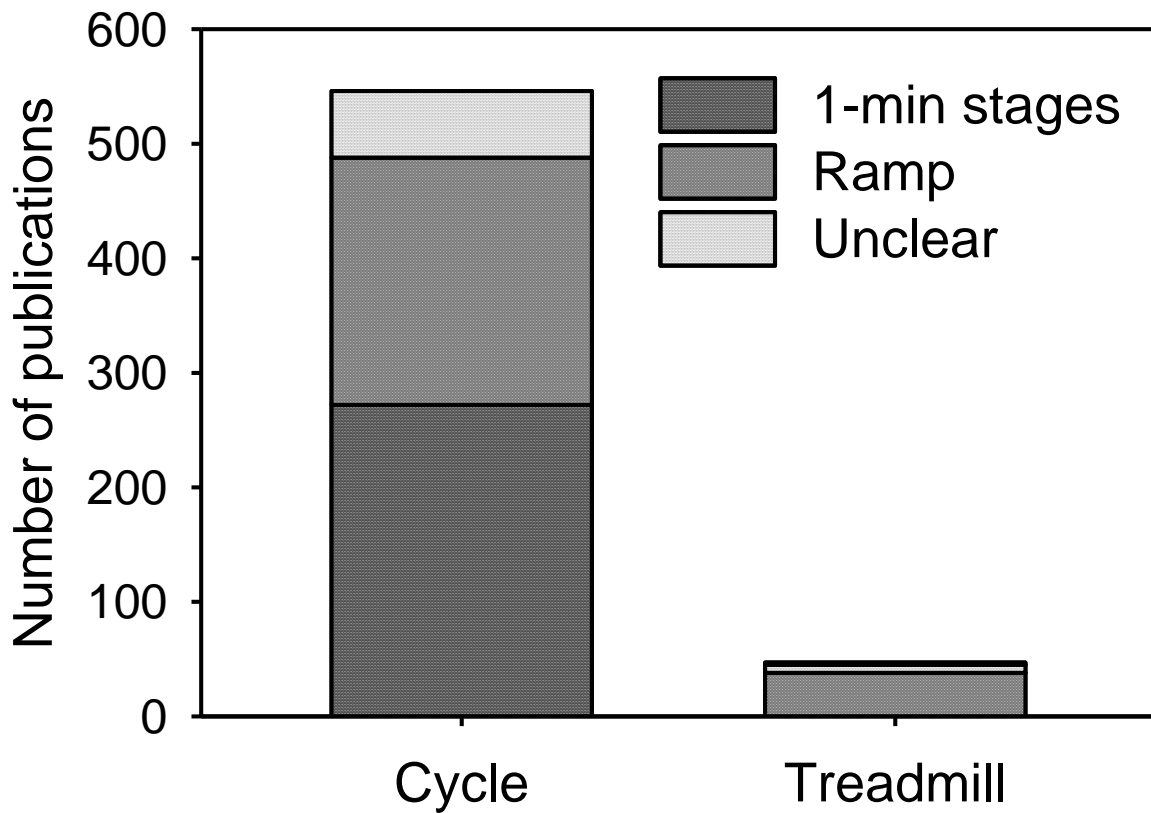
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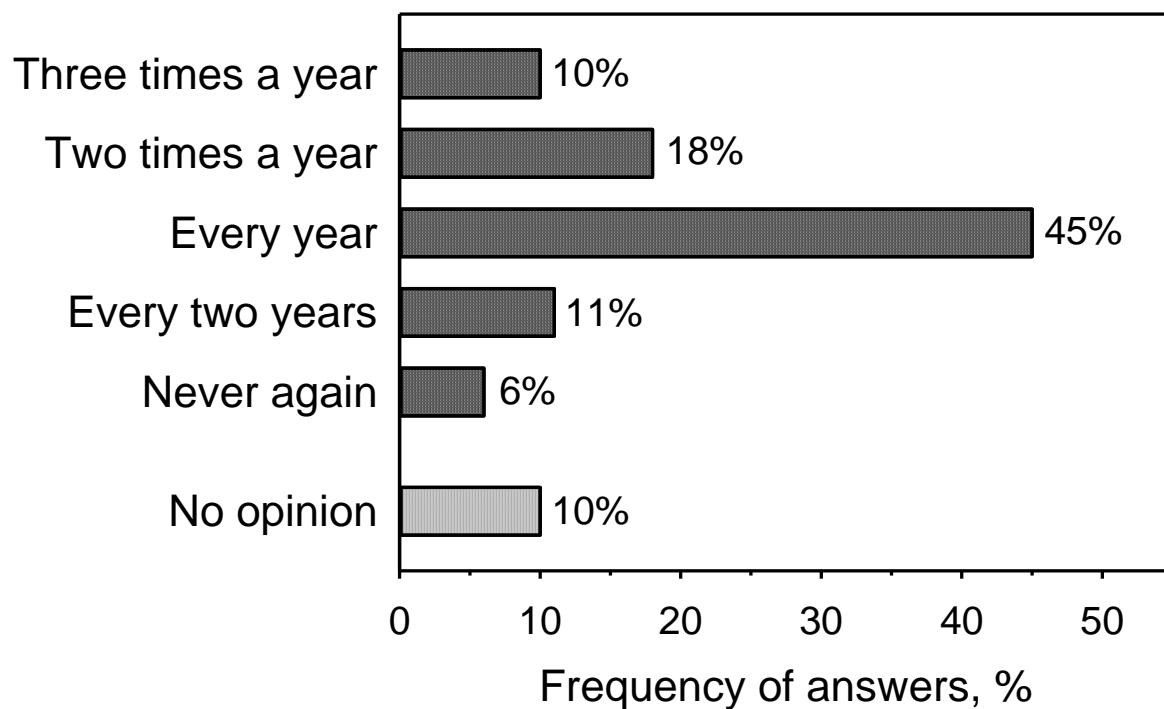
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Figure legends

Figure 1. Number of publications reporting use of cycle ergometry versus treadmill exercise protocols: results from the systematic literature review.

Figure 2. Reported frequency of participating in cardiopulmonary exercise testing in the future: results from the patient survey





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Kinesiology and Rehabilitation Sciences, Division of Respiratory Rehabilitation, Department of

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Unidade de Fisiologia Pulmonar, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio

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