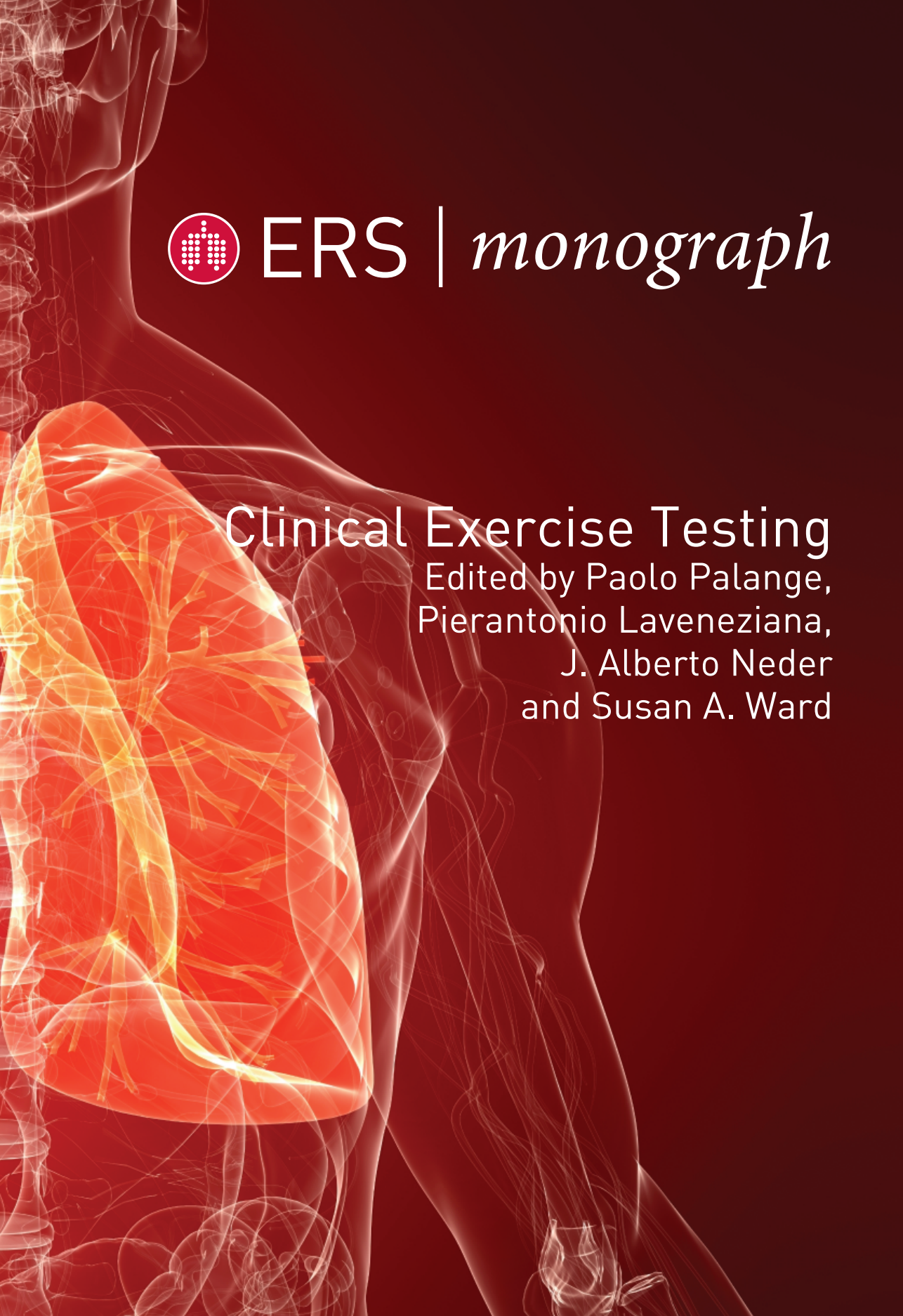
ERS | monograph
Clinical Exercise Testing
Edited by Paolo Palange,
Pierantonio Laveneziana,
J. Alberto Neder
and Susan A. Ward

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Editor in Chief
Robert Bals

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

ERS Monographs are available online at www.books.ersjournals.com and print copies are available from www.ersbookshop.com

Managing Editor: Rachel Gozzard
European Respiratory Society, 442 Glossop Road, Sheffield, S10 2PX, UK
Tel: 44 114 2672860 | E-mail: monograph@ersj.org.uk

Published by European Respiratory Society ©2018
June 2018
Print ISBN: 978-1-84984-095-8
Online ISBN: 978-1-84984-096-5
Print ISSN: 2312-508X
Online ISSN: 2312-5098
Typesetting by Nova Techset Private Limited
Printed by Charlesworth Press

ERS | monograph

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Number 80
June 2018

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Preface

Robert Bals

CPET is one of the most useful and informative diagnostic approaches in pulmonary medicine. It offers deep insight into the cardiopulmonary network and generates data that can be used in diagnosis, staging and outcome prediction in multiple lung diseases. In the hands of an experienced investigator, exercise testing looks easy and elegant. For the patient, exercise testing focuses on relevant outcomes, such as exercise capacity and dyspnoea. It also has the benefit of being noninvasive.

However, for novices in this area, the large amount of information generated and the task of interpreting this data can cause a sense of reluctance. The data that result from exercise testing differ in complexity, ranging from simple one-figure measurements to graphical displays of time curves requiring sophisticated interpretation of. As a result, a comprehensive summary of the methodology of CPET is urgently needed to ensure its more frequent use in clinical practice.

This *ERS Monograph* is therefore timely as it provides the reader with a broad and detailed overview of the various CPET applications. The initial chapters summarise the technologies and standard techniques used. They are followed by sections about individual disease areas and a chapter on lung transplantation. Self-assessment cases have also been included in this book, a first for the *ERS Monograph* book series. We hope that our readers like this new feature and will find it useful.

The Guest Editors Paolo Palange, Pierantonio Laveneziana, J. Alberto Neder and Susan A. Ward have worked very hard on topic selection and to integrate these aspects into a book that summarises current knowledge. Together with the authors, they have produced a practice-guideline publication that comprises both background information and hands-on application. I am sure this comprehensive review will be useful in the clinical practice of a broad range of respiratory physicians, and will improve patient care.

Disclosures: R. Bals has received grants from the German Research Ministerium and the Deutsche Forschungsgemeinschaft. He has also received personal fees from GSK, AstraZeneca, Boehringer Ingelheim and CSL Behring.

 Print ISBN: 978-1-84984-095-8. Online ISBN: 978-1-84984-096-5. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

Guest Editors

Paolo Palange

Paolo Palange is currently Full Professor of Respiratory Medicine at the Sapienza University of Rome (Rome, Italy) and Head of the Division of Internal Medicine and Pulmonary Medicine, Adult Cystic Fibrosis programme at Policlinico Umberto I Hospital (Rome, Italy). He qualified in Medicine at the Sapienza University School of Medicine and trained in internal medicine pulmonology in Rome and at the Indiana School of Medicine (Indianapolis, IN, USA). His main clinical fields of interest are COPD, cystic fibrosis, idiopathic arterial pulmonary hypertension and asthma.

Paolo Palange is active in research in the field of CPET in respiratory (COPD, idiopathic arterial pulmonary hypertension, cystic fibrosis) and cardiovascular diseases (chronic heart failure). He has had more than 150 original papers published and has contributed to several book chapters. He has also been involved in a number ERS scientific activities, among them all of the European Respiratory Society (ERS) Task Force documents and *ERS Monographs* on cardiopulmonary exercise testing and clinical exercise testing. He has organised several ERS courses on clinical exercise testing. He has also been actively involved in the HERMES (Harmonised Education in Respiratory Medicine for European Specialists) education programme for the ERS.

Paolo Palange was Head of the ERS's Assembly for clinical physiology and integrative biology, and was Chair of the ERS School. He has acted as co-Editor of the first and second editions of the ERS Handbook of Respiratory Medicine and was a recipient of the ERS Educational Award.

Pierantonio Laveneziana

Pierantonio Laveneziana is Pulmonologist and Associate Professor of Physiology at Sorbonne Université and the University Hospital 'Pitié-Salpêtrière' in Paris, France. He is Director of the Dyspnoea and Exercise programme at the Respiratory Department of the University Hospital 'Pitié-Salpêtrière' and at the research unit UMRS 1158 at Sorbonne Université.

 Print ISBN: 978-1-84984-095-8. Online ISBN: 978-1-84984-096-5. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

 https://doi.org/10.1183/2312508X.10017818

Pierantonio Laveneziana gained his medical degree in 2002 and his doctorate in 2012. Since then, he has worked under leaders in the field at the following prominent research laboratories: P. Palange at Sapienza University of Rome, Rome, Italy; G. Scano at the University of Florence, Florence, Italy; D. O'Donnell at Queen's University, Kingston, ON, Canada; U. Jorde at Columbia University, New York, NY, USA; M. Humbert at the National Center for Pulmonary Hypertension, Kremlin Bicêtre, Paris, France; and T. Similowski and C. Straus at Sorbonne Université and the University Hospital 'Pitié-Salpêtrière'. He was the recipient of an Investigator Award from the 5th World Symposium on Pulmonary Hypertension (2013), and a Marie Curie Actions - International Re-integration Grant (2010–2012). From 2014 to 2015, he was Associate Professor of Respiratory Medicine (2014–2015) at the Sorbonne Université and University Hospital 'Pitié-Salpêtrière'.

Pierantonio Laveneziana has served as the Secretary (2011–2014) and Chair (2014–2017) of the Clinical Respiratory Physiology, Exercise and Functional Imaging Group of the European Respiratory Society (ERS). He is currently Secretary of the Clinical Physiology and Sleep Assembly at the ERS. He has acted as both a director and member of several ERS Task Forces.

Pierantonio Laveneziana's research focuses on the pathophysiology, mechanisms and language of dyspnoea as well as the ventilatory, respiratory mechanics and gas exchange responses to exercise and activity limitation in healthy subjects and patients with asthma, COPD, ILD, chronic heart failure, pulmonary hypertension, congenital central hypoventilation syndrome, unexplained dyspnoea and obesity. He is the author of more than 100 papers on these subjects. He is an Associate Editor of the *European Respiratory Review* and a member of the Editorial Boards of the *European Respiratory Journal*, the *Journal of COPD* and more than 20 other peer-reviewed journals.

J. Alberto Neder

J. Alberto Neder is currently Professor of Medicine at Queen's University (Kingston, ON, Canada) and is a staff respirologist at the Kingston Health Sciences Centre (KHSC; Kingston, ON, Canada). He is the Director of the KHSC's Laboratory of Clinical Exercise Physiology and the Laboratory of Pulmonary Function Tests.

J. Alberto Neder has a PhD in Clinical Physiology, which was complemented by post-doctoral experiences at the University of London (London, UK) under B.J. Whipp, and the University of Glasgow (Glasgow, UK), under S.A. Ward.

J. Alberto Neder is a physician scientist with a specific interest in the cardiocirculatory and respiratory interactions that support O_2 transfer from atmospheric air to cell mitochondria. Using physical exercise as a systemic stressor, J. Alberto Neder and his associates have been successful in elucidating the mechanisms and consequences of abnormal O_2 delivery and use in chronic cardiopulmonary diseases. These lines of research have the ultimate goal of developing and testing novel pharmacological and non-pharmacological interventions to improve patient quality of life.

J. Alberto Neder has acted as a senior author on over 200 peer-reviewed papers and has authored many book chapters on respiratory and exercise physiology, pulmonary rehabilitation and integrated care in chronic respiratory diseases. His book *Clinical Exercise Physiology: Theory and Practice* is widely used as a reference text in his home country of Brazil and remains the only Portuguese-language textbook in the field. He has extensive experience in training research personnel from undergraduate to post-doctoral levels.

J. Alberto Neder's clinical and teaching interests include COPD, COPD–heart failure overlap, cardiac and pulmonary rehabilitation, pulmonary hypertension and pulmonary vascular disease, lung function and CPET.

Susan A. Ward

Susan A. Ward gained her DPhil in Physiology from Oxford University (Oxford, UK) in 1974. Following 2 years as a Lecturer in the Department of Physiology at Liverpool University (Liverpool, UK), she moved to the University of California at Los Angeles (CA, USA), becoming Professor of Anesthesiology and Physiology in 1988. She returned to the UK in 1993, first to the Department of Physiology at the University of London's St George's Hospital Medical School (London), then to South Bank University (London) as Chair of Sports Science and, in 1998, to the University of Glasgow (Glasgow) as Director of the Centre for Exercise Science and Medicine. In 2003, she was appointed Chair of Sport and Exercise Science and Head of the School of Sport and Exercise Sciences at the University of Leeds (Leeds, UK), and then Emeritus Professor in 2007. She presently operates a research and educational consultancy.

Susan A. Ward's research interests include the control of ventilation, pulmonary gas exchange and muscle energetics during exercise in health, altered environments and disease, and she has some 170 publications on these topics. She is a Fellow of the American College of Sports Medicine, the European

https://doi.org/10.1183/2312508X.10017818

Respiratory Society (ERS) and, by invitation, the European College of Sports Science.

Susan A. Ward is immediate past Editor-in-Chief of the *European Journal of Applied Physiology*. She previously served as Chair of the Pulmonary Circulation, Gas Exchange and Exercise Group of the ERS. She is a consultant for Xtreme Everest 2 (www.xtreme-everest.co.uk), a collaborative venture between Duke University (Durham, NC, USA) and the University of Southampton (Southampton, UK) and University College London (London, UK).

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Introduction: CPET in clinical practice. Recent advances, current challenges and future directions

J. Alberto Neder[1], Pierantonio Laveneziana[2,3], Susan A. Ward[4] and Paolo Palange[5,6,7,8]

This introductory chapter aims to answer three key questions germane to the uses of CPET in respiratory practice. 1) In the past 10 years, what have been the specific scenarios in which CPET has advanced the provision of clinical information valuable to decision making? 2) What are the current challenges facing clinical CPET interpretation? 3) What are the key gaps in knowledge that deserve special attention in the next 10 years in order to expand CPET application in clinical settings? Each of these pertinent questions is answered in the context of the main indications for CPET, *i.e.* investigation of exercise intolerance and dyspnoea, risk assessment, and outcome evaluation of therapeutic interventions.

Background

The European Respiratory Society (ERS) has an established track record in producing publications that focus on clinical exercise testing applied to the management of chronic lung diseases. Following the seminal ERS Task Force guidelines published in 1997 [1] and updated in 2007 [2], previous *ERS Monographs* on Clinical Exercise Testing proved influential in shaping the field [3, 4]. These efforts contributed to the dissemination of the message that, in the appropriate clinical context, CPET does add clinically relevant information. In fact, computerised "metabolic" systems are now available in most advanced pulmonary function laboratories worldwide. As shown in figure 1, 3541 of the 5100 (~70%) manuscripts involving CPET since 1978 have been published in the past 10 years (Web of Science; https://apps.webofknowledge.com). This not only indicates that a new *Monograph* is timely but that it is also poised to attract a larger readership compared to previous editions.

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 Print ISBN: 978-1-84984-095-8. Online ISBN: 978-1-84984-096-5. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

 https://doi.org/10.1183/2312508X.10015318

The 2007 *Monograph* cogently pointed out that CPET should be viewed as an adjunct to previous comprehensive medical evaluation comprising of: medical history, physical examination and, according to the specific clinical scenario, appropriate complementary tests (*e.g.* haematocrit, resting ECG, chest imaging, arterial blood–gas and acid–base status, resting pulmonary function, echocardiography) [4]. Thus, there is a key interpretative feature of CPET which, if ignored, may constitute an important source of frustration for the requesting physician: the test should always be interpreted in the light of the pre-test likelihood of abnormality. In fact, many patients referred for CPET have undergone extensive investigations, including chest computed tomography, transthoracic echocardiography and measurement of circulating biomarkers (*e.g.* troponin, brain natriuretic peptide). It is therefore the referring physician's task to integrate the described pattern(s) of dysfunction into his/her diagnostic plan or prognostic assessment. This has become even more relevant in the past decade as the "typical" patient currently referred to CPET has multiple comorbidities in addition to polypharmacy, obesity and extreme sedentarism. It follows that the individual showing a single mechanism of exercise intolerance has become exceedingly rare in the CPET laboratory.

In this challenging scenario, this *Monograph* aims to provide a comprehensive update on the contemporary uses of CPET to answer clinically relevant questions in respiratory medicine. This introduction to the *Monograph* provides a succinct overview of the key extant gaps in knowledge; the application of CPET-based investigations in these gaps might prove valuable to the improvement of patient care.

What are the specific scenarios in which CPET has advanced the provision of clinically relevant information in the past decade?

Investigating exercise intolerance

Dyspnoea as a cause of exercise intolerance

In respirology practice, CPET is now more commonly requested as part of the work-up for unexplained or disproportionate exertional dyspnoea [5–13]. As discussed elsewhere in this *Monograph* [14], the test is more suited to describing patterns of dysfunction, as different clusters of abnormalities overlap across specific diseases. CPET fundamentally aims to shorten the list of differential diagnoses that could explain a patient's symptoms; in some circumstances, it also helps guide further investigations. Results might also give reassurance that major dysfunction is not currently impacting on exercise responses.

In patients with known cardio-respiratory diseases, gaining insight into the pathophysiology of dyspnoea and exercise limitation might prove valuable to clinical decision making, particularly in patients with only mild-to-moderate disease. CPET may help clinicians unmask the physiological mechanisms (and their interactions) underlying this symptom in a broad spectrum of cardio-respiratory disorders (figure 2) [6]. The test may also help clinicians identify additional mechanisms leading to dyspnoea deemed "independent of" or "not directly related to" the disease under consideration. It can also be used to explore the mechanisms by which exertional dyspnoea can be ameliorated after pharmacological and non-pharmacological interventions [15]; a chapter by O'Donnell *et al.* [16] in this *Monograph* considers this area further.

Recognition that useful insights into the mechanical underpinnings of dyspnoea are gained by following the operating lung volumes [17] has proved important in enhancing the test's

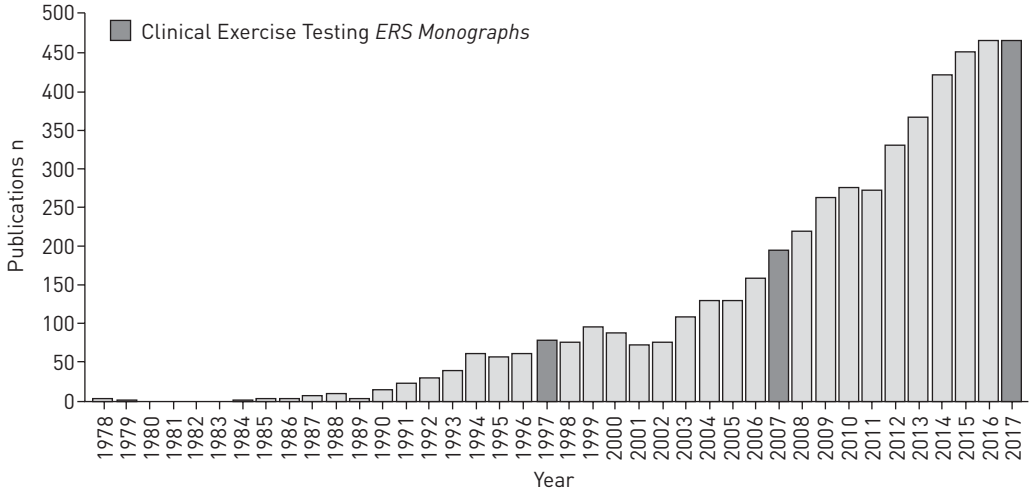

Figure 1. Number of publications on CPET indexed in the Web of Science (https://apps.webofknowledge.com) since 1978. Note that 70% were published in the past 10 years. The content of the current *ERS Monograph* (published in 2018) is based on literature published up to the end of 2017.

ability to explain exercise intolerance [18]. Specifically, it has been recognised that constraints to *V*T expansion [19], as determined by a critical IRV, are paramount to exertional dyspnoea in obstructive and restrictive lung diseases [20]; this is considered further in chapters about COPD [21] and ILD [22] later in this *Monograph*. In this context, the strengths and limitations of performing IC manoeuvres to uncover these constraints are now better recognised compared with 10 years ago. A great deal of work has helped better standardise this approach as well as the strategies used to interpret the derived variables (as reviewed in [23]). Exercise IC manoeuvres also allow tidal flow–volume loops to be correctly placed relative the maximum pre-exercise loop, thereby allowing better recognition of expiratory flow limitation [24]. Owing to these advances, most of the commercially available CPET systems now offer IC recording with tidal-to-maximal flow–volume loop displays.

Another pathophysiological feature that is important to the genesis of dyspnoea is excess exercise ventilation ("ventilatory inefficiency") as reflected by increased V'_E as a function of metabolic demand (*i.e.* V'_{CO_2}) (a chapter by WARD [25] in this *Monograph* discusses the determinants of physiological responses to muscular exercise in healthy subjects). The potential for high indices of ventilatory inefficiency (V'_E–V'_{CO_2} or the minimum ventilatory equivalent (V'_E/V'_{CO_2min})) to trigger uncomfortable respiratory sensations in cardio-respiratory disease has long been recognised [26, 27]. More recently, several studies have demonstrated that a high ventilatory inefficiency is an early sign of impaired gas exchange efficiency (increased "wasted" ventilation) and/or excessive afferent stimuli to ventilation (as recently reviewed in [28]) as it is related to a high respiratory neural drive and dyspnoea in symptomatic smokers [29, 30] and patients with mild COPD [31, 32], heart failure [8], heart failure–COPD [33, 34], ILD [35] and pulmonary hypertension (PH) [36, 37]. Thus, the use of different indices of the V'_E–V'_{CO_2} relationship has proved useful in the interpretation of CPET responses in patients with unexplained or disproportionate exertional dyspnoea [38].

Investigating potential pulmonary vascular disease

In the past decade, pulmonary vascular disease, particularly PH, has been more frequently recognised as a cause of exertional dyspnoea [36, 37]. Several studies found that a cluster of

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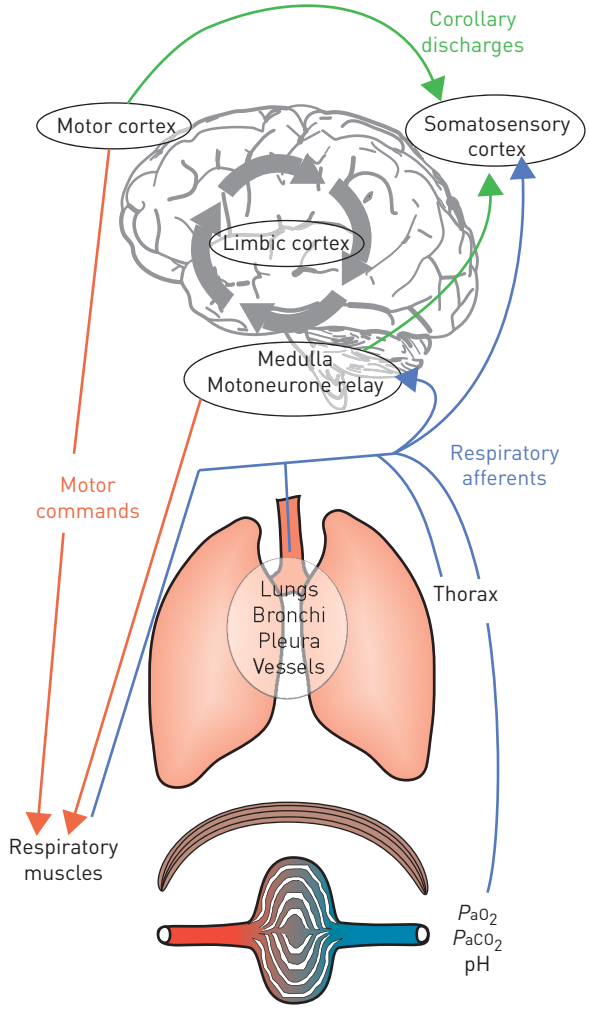

Figure 2. Integrative mechanisms at the origin of dyspnoea. Respiratory command derives from the input of both the motor cortex and the medulla. These commands are integrated at the spinal level and transmitted to the muscular effectors of the respiratory system. The subsequent activation of the respiratory muscles will generate afferent inputs that are fed back to the respiratory command centres and the somatosensory cortex. The comparison of the corollary discharge and the ensuing afferent feedback may present a mismatch, and dyspnoea will occur when a negative effect is attributed to this mismatch by the limbic cortex, which will also be influenced and modulated by memory and the prevailing environment. Reproduced and modified from [6] with permission.

CPET findings indicative of combined metabolic–cardiovascular (*e.g.* low $\Delta V'_{CO_2}/\Delta WR$, an O_2 pulse plateau, early θL) and ventilatory gas exchange abnormalities (high V'_E–V'_{CO_2} indices, low P_{ETCO_2}) suggest pulmonary vascular disease in patients with a high pre-test likelihood of disease [36, 37]; pulmonary vascular diseases are considered further later in this *Monograph* [39]. Atypically high V'_E–V'_{CO_2} indices in a COPD patient in whom there is no anatomic cause for increased wasted ventilation (*e.g.*, extensive emphysema) [40] and/or a low P_{aCO_2} set-point (*e.g.* selected patients with associated heart failure) [41] might also prompt further investigation to rule out PH [42, 43]. Conversely, a test showing a normal V'_E–V'_{CO_2} indices and P_{ETCO_2} (values and trajectory) can reassure that "significant" PH is

unlikely in an individual at risk, *e.g.* with residual exercise intolerance after pulmonary embolism [44–46].

CPET as an adjunct to the investigation of ischaemic heart disease

There is some limited evidence that a downward deflection of the $V'O_2$–WR relationship and a plateau in the O_2 pulse profile are occasionally associated with ischaemic heart disease [47, 48], as discussed later in this *Monograph* [49]. Concomitant (or subsequent) ECG abnormalities may occur, particularly in more advanced disease [50]. Although there are other more sensitive and specific modalities to investigate coronary artery disease, those abnormalities should be valued in an individual at risk.

CPET to uncover dysfunctional breathing and/or hyperventilation

Non-physiological changes and increased variability in breathing pattern, which are frequently accompanied by varied degrees of alveolar hyperventilation, can be identified in patients undergoing CPET due to unexplained dyspnoea [51–53]. Although those abnormalities are not always idiopathic (*i.e.* "primary") [54], once identified they might avoid potentially iatrogenic and costly procedures in patients who have frequently been extensively investigated.

Risk assessment

Prognosis in cardiopulmonary diseases

As a consequence of marked advances in the pharmacological and non-pharmacological treatment of heart failure in the past 10 years [55], there have been substantial changes in the variables (and their cut-offs) for predicting poor outcome (as detailed later in this *Monograph*, in chapters covering responses that are diagnostic for cardiac diseases [49] and exercise testing in the evaluation of lung and heart disease patients [56]). For example, lower peak $V'O_2$ thresholds compared with those used in seminal studies [57] are now used in multi-parametric models of risk estimation [58, 59]. A flattening submaximal $V'O_2$ trajectory has been shown to be useful to predict poor prognosis in heart failure with either reduced, mid-range or preserved ejection fraction [60]. Moreover, submaximal ventilatory (high $V'E$–$V'CO_2$ indices, oscillatory ventilation) and gas exchange variables (low $PETCO_2$) have been recognised as independent predictors of poor prognosis [61]. Similar variables (with the exception of oscillatory ventilation) have proved valuable as prognosticators in PAH [62]. Limited evidence suggests that high excessive exertional ventilation also predicts poor outcome in COPD (in association with resting hyperinflation) [63] and ILD (in association with low peak exercise capacity and mechanical constraints) [35].

Pre-operative assessment

In the pre-operative assessment of lung resection surgery, some more recent reports described a role for high $V'E$–$V'CO_2$ indices in the prediction of a negative outcome in patients with intermediate peak $V'O_2$ values [64, 65]; Harvie and Levett [66] provide a chapter on pre-operative evaluation (including lung transplantation) later in this *Monograph*. The value of traditional variables previously found to be useful in the pre-operative assessment of major abdominal surgery (low peak $V'O_2$ and/or $V'O_2\Theta T$) has been extended to colorectal, hepatobiliary, urological and abdominal aortic aneurysm surgery (as recently reviewed in [67, 68]).

 https://doi.org/10.1183/2312508X.10015318

Effects of interventions

Constant WR testing

Assessment of the tolerance of constant WR exercise pre- and post-interventions, usually accompanied by non-invasive evaluation of lung mechanics (serial IC measurements) and dyspnoea, has been more widely used in patients with COPD (the role of exercise testing in defining the response to COPD interventions is discussed in a chapter by O'Donnell *et al.* [16] later in this *Monograph*). There has also been renewed interest (albeit to a lesser extent) in the same testing modality for assessing the effects of interventions in patients with ILD, PAH and cystic fibrosis (as reviewed in [15]).

Incremental exercise testing

Changes in the submaximal responses to incremental exercise, particularly those reflecting improved O_2 delivery and lower ventilatory demands, have been more frequently used to demonstrate the beneficial effects of selected interventions in pulmonary vascular disease, *e.g.* sildenafil in PAH [69] and heart failure with reduced ejection fraction [70], calcium channel blockers in selected patients with idiopathic PAH [71], and vasodilators and thromboendarterectomy in chronic thromboembolic pulmonary hypertension [72, 73]. The incremental protocol has also been used to detect the effects of cardiovascular medications in heart failure with reduced and preserved ejection fraction, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, different types of β-blockers and sildenafil (as reviewed in [58]).

What are the current challenges facing clinical CPET interpretation?

Investigation of exercise intolerance

The patient with multiple potential causes of exercise intolerance

As previously mentioned, the patient with isolated respiratory or cardiovascular causes of exercise intolerance is an uncommon client of modern clinical CPET laboratories. It is more common for patients to have multiple comorbidities whose individual contribution to exertional symptoms is difficult to ascertain, particularly against a background of polypharmacy. This complex combination of abnormalities was less prevalent (and complex) some decades ago when CPET was initially used to uncover the "main" mechanism of exercise intolerance in subjects with unexplained dyspnoea [74–77].

The emergence of "novel" causes of exercise intolerance

The burden of obesity [78] and extreme sedentarism [79] has markedly increased in the past few decades worldwide. It follows that the boundaries between heart–lung disease and the physiological consequences of these contemporary changes have become difficult to discriminate in individual patients. It is worth noting that nowadays, many patients are referred to CPET with pre-existing abnormalities whose individual contribution to exertional symptoms remains largely unknown, *e.g.* metabolic syndrome [80], exercise-induced diastolic dysfunction [81], atrial fibrillation [82], left atrial abnormalities [83, 84], isolated respiratory muscle weakness [85] and chronotropic incompetence [86].

The limitations of noninvasive CPET in the identification of cardiocirculatory causes of exercise intolerance

Ventilatory and gas exchange variables (in addition to ECG, HR and systemic BP) are not sensitive for uncovering mild-to-moderate cardiocirculatory abnormalities on exercise [58]. For instance, flattening of the $V'O_2$/WR relationship [48] might only be evident in patients with moderate-to-severe cardiac output impairment [50]. Even in these patients, it is not uncommon to observe a late-exercise rise in $V'O_2$ due to the increased metabolic cost of ventilation in morbidly obese subjects [87] and those with respiratory comorbidity [20]. Thus, a plateau in the $V'O_2$/WR plateau might not be clearly discernible, particularly in a short test. Interpretation of the O_2 pulse has also become more complex in the past decade because of the growing prevalence of patients whose exertional HR is under pharmacological (β-blocker, ivabradine) or non-pharmacological (pacemaker) control. Anaemia and/or hypoxaemia may severely decrease arterial O_2 content, making O_2 pulse interpretation particularly challenging in a physically unfit patient. In some patients with unexplained exercise intolerance, an abnormally low cardiac output is not mechanistically linked to intrinsic cardiopulmonary disease but a failure to increase right atrial pressure, *i.e.* reduced pre-load [88].

It is also important to recognise that there are "central cardiovascular" causes of dyspnoea that are not associated with substantial impairment in stroke volume and/or cardiac output, *e.g.* heart failure with preserved ejection fraction [89, 90], exercise-induced PH [91] and right ventricle-to-pulmonary circulation uncoupling [58]. Thus, CPET variables reflecting "downstream" consequences of impaired O_2 delivery might be insensitive to these common abnormalities. In this context, measurement of pulmonary haemodynamics, left ventricular filling pressures, Fick cardiac output and arterial–venous O_2 content difference might be useful in selected patients with unexplained exercise intolerance ("invasive CPET") [92, 93]. A less complex approach involves CPET in association with exercise echocardiography to assess stroke volume, diastolic function, mitral function, left ventricular outflow and dynamic pulmonary arterial pressures ("CPET imaging") [94]. For instance, right ventricle-to-pulmonary circulation uncoupling showed an important role in determining flattening of the $V'O_2$/WR relationship in patients with different cardiovascular diseases referred for exertional dyspnoea [95]. This specific haemodynamic abnormality was associated with high $V'E–V'CO_2$ indices [94] and left atrial dynamic impairment in heart failure [84] and hypertrophic cardiomyopathy [96]. Moreover, an echocardiographic E/e′ ratio of >15 at peak exercise in association with high $V'E–V'CO_2$ indices has been found useful in the diagnosis of heart failure with preserved ejection fraction in hypertensive patients with unexplained dyspnoea [97].

Risk assessment

Limitations in the prognostic assessment of cardiopulmonary diseases

The value of peak $V'O_2$ as a prognostic index in heart failure with reduced ejection fraction has been constantly re-examined; there is therefore ongoing controversy regarding the "best" peak $V'O_2$ threshold (if any) for each individual patient [58]. As outlined in a chapter by Agostoni and Cattadori [49] later in this *Monograph*, it seems unlikely that CPET variables alone can predict outcome in such a heterogenous disease. The effects of interventions on the submaximal ventilatory gas exchange variables (*e.g.* $V'E–V'CO_2$ indices, $PETCO_2$) have not been prospectively investigated in a large number of patients; their predictive role may therefore change over time depending on the specific treatment approach. Categories of progressive risk for PH patients have also been proposed based on ventilatory gas exchange variables [62]. However, the supporting evidence for the chosen cut-off remains rather limited compared with heart failure with reduced ejection fraction.

 https://doi.org/10.1183/2312508X.10015318

Limitations in pre-operative assessment

Peak $V'O_2$ is still widely used in practice for risk estimation at pre-operative assessment (as discussed in a chapter on pre-surgical evaluation later in this *Monograph* [66]). However, this is an effort-dependent variable that is influenced by peripheral factors (detraining, muscle weakness), particularly in lung cancer patients (who frequently present with associated COPD). In this context, it remains largely unknown whether a given peak $V'O_2$ carries similar prognostic information in a patient limited by "lung factors" (*i.e.* mechanical-ventilatory and gas exchange) compared with another primarily limited by peripheral abnormalities. Due to the effects of obesity in increasing $V'O_2$ for a given WR (as discussed in a chapter by NEDER *et al.* [14] in this *Monograph*), peak $V'O_2$ might be within the "low risk" range in a patient with severely reduced peak WR; moreover, peak $V'O_2$ correction by total body weight may penalise obese subjects exercising in a cycle ergometer [98]. Submaximal variables are not free from controversies: the θL is not always identified, particularly in ventilatory-limited patients with COPD [99]. In addition, the $V'E$–$V'CO_2$ slope decreases as critical mechanical constraints progress with COPD severity [100]; thus, a relatively preserved (or even reduced) $V'E$–$V'CO_2$ slope might give false reassurance of low risk despite the presence of end-stage COPD.

Effects of interventions

The interpretation of changes in tolerance to constant WR testing

The magnitude of improvement in endurance exercise tolerance (time to intolerance (Tlim)) is influenced by the baseline Tlim [101]. This largely stems from the fact that tolerance to a given WR decreases hyperbolically above an individual's highest sustainable WR. *i.e.* critical power (CP) [102]. Thus, Tlim is expected to vary greatly among subjects depending on where the selected WR lies in the individual's power–duration relationship [103]. For instance, if the pre-intervention WR is substantially above the CP, Tlim might be excessively short. Conversely, a sub-CP test can be sustained for prolonged periods of time. If the intervention increases CP, a test performed just above this parameter is biased to "respond" to a greater extent than the other tests, *i.e.* regardless of the magnitude of the true physiological effect. Under these circumstances, the meaning of a given absolute (s) or relative (%) change in Tlim after an intervention might be difficult to interpret across subjects [103].

The MCID for the constant WR test

Despite some valuable attempts in defining the MCID for Tlim in COPD (*e.g.* a 100-s or 33% increase from baseline) [104], these thresholds have not been prospectively validated in COPD or other clinical populations. In fact, it is conceivable that the MCID varies according to patient's baseline Tlim, a complex issue that also complicates the interpretation of changes in lung function over time [105].

What are the key gaps in the knowledge that need to be addressed in the next 10 years to expand CPET application in the clinical arena?

CPET in the investigation of exercise intolerance: the key unmet clinical needs

Table 1 presents a list of research areas that should be considered in the future investigation of exercise intolerance.

The current limitations relating to the reference values for CPET either in adults or children are not trivial, and are considered in greater detail in chapters by Puente-Maestu *et al.* [106] and Burghard *et al.* [107], respectively, elsewhere in this *Monograph*. In this context, a global frame of reference (akin to the ERS-sponsored Global Lung Initiative for pulmonary function tests [105]) based on a large number of subjects with a broad span of age and body dimensions, and matched for habitual physical activity level, would be particularly useful to enhance test interpretation. This also applies to the interpretation of symptom burden: comprehensive reference intervals for Borg dyspnoea scores as a function of WR [108] and ventilation, for instance, are not yet available. There is a noticeable paucity of normal values for treadmill-based tests. In fact, there is an urgent need to

Table 1. Suggested avenues for patient-oriented research in the next 10 years; the outcomes of such research may enhance the clinical applicability of CPET in respiratory medicine

Investigation of exercise intolerance

A global frame of reference for key metabolic, ventilatory and cardiovascular variables in response to standardised cycle ergometer and treadmill protocols

Large normative standards for the trajectory of exertional symptoms as a function of exercise intensity (WR) and physiological demands (V'_{O_2} and V'_E)

Prospective, multicentre studies addressing the role of CPET in discriminating syndromes of exercise limitation in contemporary clinical populations with multiple co-existing diseases

Prospective, multicentre studies testing the incremental role (to commonly used metabolic and ventilatory variables) of noninvasive measurements of lung mechanics and symptoms in the investigation of exertional dyspnoea

The clinical value of adding noninvasive to minimally invasive methods to the estimation of stroke volume and P_{aCO_2}

Milder constant load protocols to investigate the mechanisms of exercise intolerance in elderly and frail patients

The role of common cardiovascular comorbidities in exertional dyspnoea in COPD and ILD

The independent role of diastolic dysfunction, left atrial enlargement, atrial fibrillation and chronotropic incompetence in respiratory symptoms in patients with unexplained dyspnoea

CPET-based criteria to differentiate chaotic/erratic breathing patterns from data noise in subjects with suspected dysfunctional breathing hyperventilation

Risk assessment

CPET variables added to multiparametric models of risk prediction

Prognostic assessment of patients with mild/early chronic respiratory disease

Risk stratification in chronic respiratory diseases other than COPD

Prospective multicentre studies to establish the actual role of CPET in addition to pulmonary function tests and field-based tests in predicting poor outcome after lung resection surgery

Addition of the syndromic mechanism of exercise limitation to physiological thresholds in order to improve the prognostic yield of CPET

Use of submaximal variables from the incremental test to predict poor outcome

Contrasting the predictive values of different metrics of ventilatory inefficiency across disease states

Effects of interventions

Strategies to optimise the use of constant WR tests to assess the effects of respiratory medication in individual patients

Feasible, pragmatic approaches to individualise the exercise intensity for endurance tests

Prospective multicentre studies to establish the MCID for changes in time to exercise intolerance in different respiratory diseases

Robust criteria to discriminate "responders" from "non-responders" regarding exercise tolerance in clinical trials

Submaximal variables from the incremental test to assess the effects of selected interventions

https://doi.org/10.1183/2312508X.10015318

address the long-standing dichotomy of cycle ergometer tests in respirology [2] *versus* treadmill tests in cardiology [61]. This separation has negatively impacted the assessment of exercise normalcy and quantification of impairment in patients who frequently present with lung and heart diseases. Prospective multicentre studies should address the role of CPET as a screening test to identify the syndromes of exercise limitation in contemporary clinical populations with multiple coexisting diseases. Improving our understanding of the confounding effects of obesity on the patterns of exercise limitation is paramount: linear time trend forecasts suggest that by 2030, 51% of the North-American population will be obese [78]. With this in mind, large investigations are specifically warranted to test the incremental role (to standard metabolic gas exchange variables) of noninvasive measurements of lung mechanics and symptoms in the clarification of the causes of exertional dyspnoea.

In view of the current limitations of CPET in unequivocally differentiating central cardiovascular from muscular-peripheral causes of exercise intolerance (further discussed by Agostoni and Cattadori [49] elsewhere in this *Monograph*) and indicating poor ventilation/perfusion matching (further discussed by Weatherald and Laveneziana [39] elsewhere in this *Monograph*), noninvasive estimates of stroke volume and $P_{a}CO_2$ (capillary or transcutaneous CO_2 tension (P_{CO_2})) might substantially improve "diagnostic" yield [109–111]. Mild, submaximal protocols might improve our ability to investigate the mechanisms of exercise intolerance in the growing population of severely disabled, elderly patients [112]. It is also crucial to address the large gaps in the knowledge relative to the independent contribution of common cardiovascular comorbidities to exertional dyspnoea in COPD and ILD. This might prove particularly helpful in conditions that are potentially associated with a high ventilatory drive secondary to increased pulmonary venous pressures such as (moderate-to-severe) diastolic dysfunction [81], left atrial enlargement [83, 84] and atrial fibrillation [82]. Last but not least, CPET-based criteria to differentiate chaotic/erratic breathing patterns from data noise would be of a great value in a specific scenario in which the test has a clear potential of impacting on clinical decision making [10] (abnormals patterns of response are discussed further later in this *Monograph* [14].

CPET for risk assessment: the key unmet clinical needs

Table 1 presents a list of research areas that should be considered in the future investigation of risk assessment.

Exercise responses may be more helpful in adding prognostic information to resting data in patients with more preserved lung function. There is therefore a need to prospectively test the prognostic value of CPET variables in patients with only mild or early chronic respiratory disease. Few data are currently available regarding the use of CPET for risk stratification in diseases other than COPD. Regardless of the specific disease, CPET variables are more likely to prove useful if added to multiparametric models of risk prediction, such as those developed for patients with heart failure with reduced ejection fraction [58, 59].

In the pre-operative assessment of lung resection surgery, more research is needed to clarify the precise role of CPET in relation to imaging (*e.g.* scintigraphy) and field or walking tests (Singh and Harvey-Dunstan [113] consider walking in the assessment of COPD patients later in this *Monograph*). Variables deemed to reflect exercise (in)tolerance, such as peak $V'O_2$, are likely to be more informative if analysed in conjunction with potentially limiting

mechanism(s). For instance, a low peak $V'O_2$ due to severe mechanical constraints in a patient with COPD probably signals a higher pre-operative risk than a similar value obtained in a detrained patient with ample mechanical-ventilatory reserves. With the exception of the $V'E$–$V'CO_2$ relationship [59], little attention has been given to the ability of the submaximal variables from the incremental test to predict poor outcome. The best metric of ventilatory inefficiency for prognosis estimation is currently unclear [26]. For instance, it is possible that additional information is gained from the $V'E$–$V'CO_2$ intercept or $V'E/V'CO_2$min rather than the $V'E$–$V'CO_2$ slope, particularly in mechanically limited patients with COPD and lung cancer. A negative $V'E$ intercept in a patient with combined heart or pulmonary vascular disease signals a particularly high ventilatory drive, which is a potent marker of poor prognosis in cardiovascular disease.

CPET to assess the effects of interventions: the key unmet clinical needs

Table 1 presents a list of research areas that should be considered in the future investigation of the effects of interventions.

Constant WR tests are rarely used in practice (with the exception of clinical trials), partially because little is known about how to integrate this information into decision making for individual patients. The surmounting complexities in determining an individual's CP are unlikely to be solved in clinical populations [103]; feasible approaches to the individualisation of exercise intensity for endurance tests are therefore warranted [114, 115]. Such pragmatic approaches might reduce the pre-intervention variability on Tlim, thereby decreasing the sample size for interventional studies while aiding the interpretation of changes [116]. Establishing robust criteria for CPET responders *versus* non-responders would be valuable to titrate medications with a variable effect on exercise tolerance, such as bronchodilators in COPD [117] and β-blockers in heart failure with reduced ejection fraction [58]. In addition, submaximal variables from the incremental test have been largely neglected in assessing the effects of interventions. This unmet need is particularly relevant in practice as the incremental test is the only testing modality that is reimbursed in many countries.

Conclusion

As with any other topic, the potential usefulness of a clinical method of investigation should be cautiously analysed in light of its current limitations. Such a sober and unbiased approach is a crucial step in order to open real perspectives of improvement. Despite the relevant advances outlined here, the authors recognise that CPET remains largely undervalued and, therefore, underused in respiratory medicine worldwide. We hope that at least part of the challenges facing contemporary CPET may be addressed in the next 10 years (table 1), thereby expanding its clinical application in respiratory medicine. At this time, and considering the contemporary trends of increasing obesity, sedentarism, polypharmacy and psychogenic causes of dyspnoea, it seems plausible that CPET will be more frequently used in association with other noninvasive to minimally invasive [94, 109, 111, 118, 119] and, in some selected cases, invasive methods [92]. In this context, the assessment and management of patients with exercise intolerance and dyspnoea would benefit greatly from a new generation of modular "metabolic" systems with the capabilities of measuring key cardiovascular (*e.g.* noninvasive stroke volume and cardiac output), pulmonary gas exchange (*e.g.* estimated $PaCO_2$ and dead space ventilation) and sensory responses (continuous dyspnoea readings). The field would also greatly benefit from

 https://doi.org/10.1183/2312508X.10015318

concerted and unified approaches to CPET, combining the efforts of major cardiological and respiratory societies, including the American College of Chest Physicians (CHEST), the American Heart Association (AHA), the American Thoracic Society (ATS), the European Association for Cardiovascular Prevention and Rehabilitation (EACPR), the European Society of Cardiology (ESC) and ERS.

References

1. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. *Eur Respir J*. 1997; 10: 2662–2689.
2. Palange P, Ward SA, Carlsen K-H, *et al.* Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29: 185–209.
3. Roca J, Whipp BJ, eds. Clinical Exercise Testing (European Respiratory Monograph). Sheffield, European Respiratory Society, 1997.
4. Ward SA, Palange P, eds. Clinical Exercise Testing (European Respiratory Monograph). Sheffield, European Respiratory Society, 2007.
5. Mahler DA, Horowitz MB. Clinical evaluation of exertional dyspnea. *Clin Chest Med* 1994; 15: 259–269.
6. Laviolette L, Laveneziana P. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J* 2014; 43: 1750–1762.
7. O'Donnell DE, Elbehairy AF, Faisal A, *et al.* Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing. *Eur Respir Rev* 2016; 25: 333–347.
8. Dubé B-P, Agostoni P, Laveneziana P. Exertional dyspnoea in chronic heart failure: the role of the lung and respiratory mechanical factors. *Eur Respir Rev* 2016; 25: 317–332.
9. Bernhardt V, Babb TG. Exertional dyspnoea in obesity. *Eur Respir Rev* 2016; 25: 487–495.
10. Depiazzi J, Everard ML. Dysfunctional breathing and reaching one's physiological limit as causes of exercise-induced dyspnoea. *Breathe* 2016; 12: 120–129.
11. Bonini M, Fiorenzano G. Exertional dyspnoea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing. *Eur Respir Rev* 2017; 26: 160099.
12. Berliner D, Schneider N, Welte T, *et al.* The differential diagnosis of dyspnea. *Dtsch Arzteblatt Int* 2016; 113: 834–845.
13. Mahler DA. Evaluation of dyspnea in the elderly. *Clin Geriatr Med* 2017; 33: 503–521.
14. Neder JA, Berton DC, Rocha A, *et al.* Abnormal patterns of response to incremental CPET. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 34–58.
15. Puente-Maestu L, Palange P, Casaburi R, *et al.* Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur Respir J* 2016; 47: 429–460.
16. O'Donnell DE, Elbehairy AF, Berton DC, *et al.* Exercise testing in the evaluation of pharmacotherapy in COPD. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 235–250.
17. O'Donnell DE, Webb KA. The major limitation to exercise performance in COPD is dynamic hyperinflation. *J Appl Physiol Bethesda Md 1985* 2008; 105: 753–755.
18. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
19. Laveneziana P, Webb KA, Ora J, *et al.* Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am J Respir Crit Care Med* 2011; 184: 1367–1373.
20. O'Donnell DE, Laveneziana P, Webb K, *et al.* Chronic obstructive pulmonary disease: clinical integrative physiology. *Clin Chest Med* 2014; 35: 51–69.
21. O'Donnell DE, Elbehairy AF, Domnik NJ, *et al.* Patterns of cardiopulmonary response to exercise in COPD. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 107–127.
22. Molgat-Seon Y, Guenette JA, Schaeffer MR, *et al.* Patterns of cardiopulmonary response to exercise in fibrotic ILD. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 128–145.
23. Guenette JA, Chin RC, Cory JM, *et al.* Inspiratory capacity during exercise: measurement, analysis, and interpretation. *Pulm Med* 2013; 2013: 956081.
24. Johnson BD, Weisman IM, Zeballos RJ, *et al.* Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 1999; 116: 488–503.

25. Ward SA. Determinants of the physiological systems' response to muscular exercise in healthy subjects. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 1–33.
26. Whipp BJ, Ward SA. Cardiopulmonary coupling during exercise. *J Exp Biol* 1982; 100: 175–193.
27. Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. *Am Rev Respir Dis* 1984; 129: S17–S20.
28. Weatherald J, Sattler C, Garcia G, *et al.* Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. *Eur Respir J* 2018; 51: 1700860.
29. Elbehairy AF, Guenette JA, Faisal A, *et al.* Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 2016; 48: 694–705.
30. Barbosa GW, Neder JA, Utida K, *et al.* Impaired exercise ventilatory efficiency in smokers with low transfer factor but normal spirometry. *Eur Respir J* 2017; 49: 1602511.
31. Elbehairy AF, Ciavaglia CE, Webb KA, *et al.* Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med* 2015; 191: 1384–1394.
32. Neder JA, Berton DC, Müller PT, *et al.* Ventilatory inefficiency and exertional dyspnea in early chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2017; 14: S22–S29.
33. Apostolo A, Laveneziana P, Palange P, *et al.* Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. *Int J Cardiol* 2015; 189: 134–140.
34. Arbex FF, Alencar MC, Souza A, *et al.* Exercise ventilation in COPD: influence of systolic heart failure. *COPD* 2016; 13: 693–699.
35. Vainshelboim B, Oliveira J, Fox BD, *et al.* The prognostic role of ventilatory inefficiency and exercise capacity in idiopathic pulmonary fibrosis. *Respir Care* 2016; 61: 1100–1109.
36. Neder JA, Ramos RP, Ota-Arakaki JS, *et al.* Exercise intolerance in pulmonary arterial hypertension. The role of cardiopulmonary exercise testing. *Ann Am Thorac Soc* 2015; 12: 604–612.
37. Weatherald J, Farina S, Bruno N, *et al.* Cardiopulmonary exercise testing in pulmonary hypertension. *Ann Am Thorac Soc* 2017; 14: Suppl. 1, S84–S92.
38. Neder JA, Berton DC, Arbex FF, *et al.* Physiological and clinical relevance of exercise ventilatory efficiency in COPD. *Eur Respir J* 2017; 49: 1602036.
39. Weatherald J, Laveneziana P. Patterns of cardiopulmonary response to exercise in pulmonary vascular diseases. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 160–174.
40. Jones JH, Zelt JT, Hirai DM, *et al.* Emphysema on thoracic CT and exercise ventilatory inefficiency in mild-to-moderate COPD. *COPD* 2017; 14: 210–218.
41. Rocha A, Arbex FF, Sperandio PA, *et al.* Excess ventilation in chronic obstructive pulmonary disease-heart failure overlap: Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med* 2017; 196: 1264–1274.
42. Holverda S, Bogaard HJ, Groepenhoff H, *et al.* Cardiopulmonary exercise test characteristics in patients with chronic obstructive pulmonary disease and associated pulmonary hypertension. *Respir Int Rev Thorac Dis* 2008; 76: 160–167.
43. Boerrigter BG, Bogaard HJ, Trip P, *et al.* Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. *Chest* 2012; 142: 1166–1174.
44. McCabe C, Deboeck G, Harvey I, *et al.* Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism. *Thromb Res* 2013; 132: 659–665.
45. Ramos RP, Ferreira EVM, Valois FM, *et al.* Clinical usefulness of end-tidal CO2 profiles during incremental exercise in patients with chronic thromboembolic pulmonary hypertension. *Respir Med* 2016; 120: 70–77.
46. Godinas L, Sattler C, Lau EM, *et al.* Dead-space ventilation is linked to exercise capacity and survival in distal chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 2017; 36: 1234–1242.
47. Belardinelli R, Lacalaprice F, Carle F, *et al.* Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003; 24: 1304–1313.
48. Belardinelli R, Lacalaprice F, Tiano L, *et al.* Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. *Int J Cardiol* 2014; 174: 337–342.
49. Agostoni P, Cattadori G. Patterns of cardiopulmonary response to exercise in cardiac diseases. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 146–159.
50. Munhoz EC, Hollanda R, Vargas JP, *et al.* Flattening of oxygen pulse during exercise may detect extensive myocardial ischemia. *Med Sci Sports Exerc* 2007; 39: 1221–1226.
51. Jack S, Rossiter HB, Pearson MG, *et al.* Ventilatory responses to inhaled carbon dioxide, hypoxia, and exercise in idiopathic hyperventilation. *Am J Respir Crit Care Med* 2004; 170: 118–125.

 https://doi.org/10.1183/2312508X.10015318

52. Boulding R, Stacey R, Niven R, *et al.* Dysfunctional breathing: a review of the literature and proposal for classification. *Eur Respir Rev* 2016; 25: 287–294.
53. Neder JA, Hirai DM, Jones JH, *et al.* A 56-year-old, otherwise healthy woman presenting with light-headedness and progressive shortness of breath. *Chest* 2016; 150: e23–e27.
54. Law N, Ruane LE, Low K, *et al.* Dysfunctional breathing is more frequent in chronic obstructive pulmonary disease than in asthma and in health. *Respir Physiol Neurobiol* 2017; 247: 20–23.
55. Yancy CW, Jessup M, Bozkurt B, *et al.* 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2016; 134: e282–e293.
56. Laviolette L, Laveneziana P. Exercise testing in the prognostic evaluation of patients with lung and heart diseases. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 222–234.
57. Mancini DM, Eisen H, Kussmaul W, *et al.* Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; 83: 778–786.
58. Guazzi M, Bandera F, Ozemek C, *et al.* Cardiopulmonary exercise testing: what is its value? *J Am Coll Cardiol* 2017; 70: 1618–1636.
59. Cahalin LP, Chase P, Arena R, *et al.* A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. *Heart Fail Rev* 2013; 18: 79–94.
60. Popovic D, Arena R, Guazzi M. A flattening oxygen consumption trajectory phenotypes disease severity and poor prognosis in patients with heart failure with reduced, mid-range, and preserved ejection fraction. *Eur J Heart Fail* 2018; (DOI: 10.1002/ejhf.1140).
61. Balady GJ, Arena R, Sietsema K, *et al.* Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; 122: 191–225.
62. 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* 2016; pii: ehw180.
63. Neder JA, Alharbi A, Berton DC, *et al.* Exercise ventilatory inefficiency adds to lung function in predicting mortality in COPD. *COPD* 2016; 13: 416–424.
64. Brunelli A, Belardinelli R, Pompili C, *et al.* Minute ventilation-to-carbon dioxide output (VE/VCO2) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *Ann Thorac Surg* 2012; 93: 1802–1806.
65. Brunelli A. Ventilatory efficiency slope: an additional prognosticator after lung cancer surgery. *Eur J Cardiothorac Surg* 2016; 50: 780–781.
66. Harvie D, Levett DZH. Exercise testing for pre-operative evaluation. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 251–279.
67. Older PO, Levett DZH. Cardiopulmonary exercise testing and surgery. *Ann Am Thorac Soc* 2017; 14: Suppl. 1, S74–S83.
68. Levett DZH, Jack S, Swart M, *et al.* Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Br J Anaesth* 2018; 120: 484–500.
69. Oudiz RJ, Roveran G, Hansen JE, *et al.* Effect of sildenafil on ventilatory efficiency and exercise tolerance in pulmonary hypertension. *Eur J Heart Fail* 2007; 9: 917–921.
70. Guazzi M, Myers J, Peberdy MA, *et al.* Ventilatory efficiency and dyspnea on exertion improvements are related to reduced pulmonary pressure in heart failure patients receiving Sildenafil. *Int J Cardiol* 2010; 144: 410–412.
71. Tang Y, Yao L, Liu Z, *et al.* Effect of calcium channel blockers evaluated by cardiopulmonary exercise testing in idiopathic pulmonary arterial hypertension responding to acute pulmonary vasoreactivity testing. *Pulm Pharmacol Ther* 2017; 43: 26–31.
72. Iwase T, Nagaya N, Ando M, *et al.* Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. *Heart Br Card Soc* 2001; 86: 188–192.
73. Charalampopoulos A, Gibbs JSR, Davies RJ, *et al.* Exercise physiological responses to drug treatments in chronic thromboembolic pulmonary hypertension. *J Appl Physiol* 2016; 121: 623–628.
74. Neuberg GW, Friedman SH, Weiss MB, *et al.* Cardiopulmonary exercise testing. The clinical value of gas exchange data. *Arch Intern Med* 1988; 148: 2221–2226.
75. Palange P, Carlone S, Forte S, *et al.* Cardiopulmonary exercise testing in the evaluation of patients with ventilatory *vs* circulatory causes of reduced exercise tolerance. *Chest* 1994; 105: 1122–1126.
76. Martinez FJ, Stanopoulos I, Acero R, *et al.* Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. *Chest* 1994; 105: 168–174.
77. Flaherty KR, Wald J, Weisman IM, *et al.* Unexplained exertional limitation: characterization of patients with a mitochondrial myopathy. *Am J Respir Crit Care Med* 2001; 164: 425–432.

78. Finkelstein EA, Khavjou OA, Thompson H, *et al.* Obesity and severe obesity forecasts through 2030. *Am J Prev Med* 2012; 42: 563–570.
79. Ng SW, Popkin BM. Time use and physical activity: a shift away from movement across the globe. *Obes Rev Off J Int Assoc Study Obes* 2012; 13: 659–680.
80. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep* 2018; 20: 12.
81. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol* 2005; 46: 1883–1890.
82. Guazzi M, Belletti S, Tumminello G, *et al.* Exercise hyperventilation, dyspnea sensation, and ergoreflex activation in lone atrial fibrillation. *Am J Physiol Heart Circ Physiol* 2004; 287: H2899–H2905.
83. Aaron CP, Hoffman EA, Lima JAC, *et al.* Pulmonary vascular volume, impaired left ventricular filling and dyspnea: The MESA Lung Study. *PloS One* 2017; 12: e0176180.
84. Sugimoto T, Bandera F, Generati G, *et al.* Left atrial function dynamics during exercise in heart failure: pathophysiological implications on the right heart and exercise ventilation inefficiency. *JACC Cardiovasc Imaging* 2017; 10: 1253–1264.
85. Bonnevie T, Gravier F-E, Ducrocq A, *et al.* Exercise testing in patients with diaphragm paresis. *Respir Physiol Neurobiol* 2017; 248: 31–35.
86. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation* 2011; 123: 1010–1020.
87. Chlif M, Temfemo A, Keochkerian D, *et al.* Advanced mechanical ventilatory constraints during incremental exercise in class iii obese male subjects. *Respir Care* 2015; 60: 549–560.
88. Oldham WM, Lewis GD, Opotowsky AR, *et al.* Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. *Pulm Circ* 2016; 6: 55–62.
89. Bhella PS, Prasad A, Heinicke K, *et al.* Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2011; 13: 1296–1304.
90. Abudiab MM, Redfield MM, Melenovsky V, *et al.* Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2013; 15: 776–785.
91. Kovacs G, Herve P, Barbera JA, *et al.* An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J* 2017; 50: 1700578.
92. Huang W, Resch S, Oliveira RK, *et al.* Invasive cardiopulmonary exercise testing in the evaluation of unexplained dyspnea: Insights from a multidisciplinary dyspnea center. *Eur J Prev Cardiol* 2017; 24: 1190–1199.
93. Berry NC, Manyoo A, Oldham WM, *et al.* Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. *Pulm Circ* 2015; 5: 610–618.
94. Guazzi M, Naeije R, Arena R, *et al.* Echocardiography of right ventriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. *Chest* 2015; 148: 226–234.
95. Bandera F, Generati G, Pellegrino M, *et al.* Role of right ventricle and dynamic pulmonary hypertension on determining ΔVO2/ΔWork Rate flattening: insights from cardiopulmonary exercise test combined with exercise echocardiography. *Circ Heart Fail* 2014; 7: 782–790.
96. Finocchiaro G, Haddad F, Knowles JW, *et al.* Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: a potential role for comprehensive noninvasive hemodynamic assessment. *JACC Heart Fail* 2015; 3: 408–418.
97. Nedeljkovic I, Banovic M, Stepanovic J, *et al.* The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. *Eur J Prev Cardiol* 2016; 23: 71–77.
98. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129: S49–S55.
99. Zacarias EC, Neder JA, Cendom SP, *et al.* Heart rate at the estimated lactate threshold in patients with chronic obstructive pulmonary disease: effects on the target intensity for dynamic exercise training. *J Cardpulm Rehabil* 2000; 20: 369–376.
100. Neder JA, Arbex FF, Alencar MCN, *et al.* Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur Respir J* 2015; 45: 377–387.
101. Casaburi R, Porszasz J. Constant work rate exercise testing: a tricky measure of exercise tolerance. *COPD* 2009; 6: 317–319.
102. Neder JA, Jones PW, Nery LE, *et al.* Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease. The power-duration relationship. *Am J Respir Crit Care Med* 2000; 162: 497–504.
103. Whipp BJ, Ward SA. Quantifying intervention-related improvements in exercise tolerance. *Eur Respir J* 2009; 33: 1254–1260.
104. Puente-Maestu L, Villar F, de Miguel J, *et al.* Clinical relevance of constant power exercise duration changes in COPD. *Eur Respir J* 2009; 34: 340–345.
105. Cooper BG, Stocks J, Hall GL, *et al.* The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. *Breathe* 2017; 13: e56–e64.

 https://doi.org/10.1183/2312508X.10015318

106. Puente-Maestu L, García de Pedro J, Benedetti PA, *et al.* Reference values in adults. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 82–106.
107. Burghard M, Hulzebos EHJ, Olin JT, *et al.* Exercise testing in children with respiratory diseases. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 196–215.
108. Killian KJ, Summers E, Jones NL, *et al.* Dyspnea and leg effort during incremental cycle ergometry. *Am Rev Respir Dis* 1992; 145: 1339–1345.
109. McEvoy JD, Jones NL. Arterialized capillary blood gases in exercise studies. *Med Sci Sports* 1975; 7: 312–315.
110. Hoffmann U, Essfeld D, Stegemann J. Comparison of arterial, end-tidal and transcutaneous PCO2 during moderate exercise and external CO2 loading in humans. *Eur J Appl Physiol* 1990; 61: 1–4.
111. Stege G, van den Elshout FJJ, Heijdra YF, *et al.* Accuracy of transcutaneous carbon dioxide tension measurements during cardiopulmonary exercise testing. *Respir Int Rev Thorac Dis* 2009; 78: 147–153.
112. Bhatt DV, Kocheril AG. Submaximal cardiopulmonary exercise testing for the evaluation of unexplained dyspnea. *South Med J* 2014; 107: 144–149.
113. Singh SJ, Harvey-Dunstan TC. Walking for the assessment of patients with COPD. *In*: Palange P, Laveneziana P, Neder JA, *et al.*, eds. Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiraotry Society, 2018; pp. 175–195.
114. Malaguti C, Nery LE, Dal Corso S, *et al.* Alternative strategies for exercise critical power estimation in patients with COPD. *Eur J Appl Physiol* 2006; 96: 59–65.
115. Degani-Costa LH, O'Donnell DE, Webb K, *et al.* A simplified approach to select exercise endurance intensity for interventional studies in COPD. *COPD* 2018; (DOI: 10.1080/15412555.2018.1428944).
116. van der Vaart H, Murgatroyd SR, Rossiter HB, *et al.* Selecting constant work rates for endurance testing in COPD: the role of the power-duration relationship. *COPD* 2014; 11: 267–276.
117. Calzetta L, Rogliani P, Matera MG, *et al.* A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable COPD. *Chest* 2016; 149: 1181–1196.
118. Ferreira EM, Ota-Arakaki JS, Barbosa PB, *et al.* Signal-morphology impedance cardiography during incremental cardiopulmonary exercise testing in pulmonary arterial hypertension. *Clin Physiol Funct Imaging* 2012; 32: 343–352.
119. Agostoni P, Vignati C, Gentile P, *et al.* Reference values for peak exercise cardiac output in healthy individuals. *Chest* 2017; 151: 1329–1337.

Disclosures: J.A. Neder has received research funding *via* Queen's University from Boehringer Ingelheim and has served on speakers' bureaus, consultation panels and advisory boards for AstraZeneca, Boehringer Ingelheim and Chiesi Pharmaceutici. P. Laveneziana reports receiving personal fees from the following, outside the submitted work: Novartis France and Boehringer France.

List of abbreviations

θL	lactate threshold
6MWD	6-min walk distance
6MWT	6-min walk test
BMI	body mass index
BP	blood pressure
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
D_{LCO}	diffusing capacity of the lung for carbon monoxide
EELV	end-expiratory lung volume
EILV	end-inspiratory lung volume
FEV_1	forced expiratory volume in 1 s
FRC	functional residual capacity
FVC	forced vital capacity
HR	heart rate
IC	inspiratory capacity
ILD	interstitial lung disease
IRV	inspiratory reserve volume
MCID	minimally clinically important difference
MVV	maximum voluntary ventilation
O_2	oxygen
P_{aCO_2}	arterial carbon dioxide tension
PAH	pulmonary arterial hypertension
P_{aO_2}	arterial oxygen tension
P_{ETCO_2}	end-tidal carbon dioxide tension
P_{ETO_2}	end-tidal oxygen tension
RV	residual volume
S_{aO_2}	arterial oxygen saturation
S_{pO_2}	arterial oxygen saturation measured by pulse oximetry
t_E	expiratory time
t_I	inspiratory time
TLC	total lung capacity
$\dot{V}CO_2$	carbon dioxide output
V_D	dead space volume
V_E	expired volume
$\dot{V}_E$	minute ventilation
$\dot{V}O_2$	oxygen uptake
V_T	tidal volume
WR	work rate