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EDITORIAL: CLINICAL PHYSIOLOGY AND INTEGRATIVE BIOLOGY ASSEMBLY

The changing face of respiratory physiology: 20 years of progress within the ERS

Clinical Physiology and Integrative Biology Assembly contribution to the celebration of 20 years of the ERS

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Respiratory physiology, the study of the function of the respiratory system in health and disease, was one of the core disciplines in respiratory medicine throughout the second half of the 20th Century. Moreover, clinical and basic physiologists were central to the creation of the European Respiratory Society (ERS) 20 yrs ago. Despite concerns that all the ''interesting'' questions in physiology had been answered, the last 20 yrs have shown that applying physiological principles to respiratory disease not only leads to new insights into how the lungs work when stressed, but has also identified new areas where the diagnosis and treatment of previously intractable or unrecognised physiological disorders has transformed the lives of large numbers of people.

This editorial reflects this diversity of interest, but is only a snapshot of some of the exciting possibilities that a physiological approach to respiratory disease has made possible.

STRUCTURE, FUNCTION AND EXERCISE

By the late 1980s the key principles underpinning lung mechanics and gas exchange within the lung had been established and applied to most, but not all, problems. One orphan area was the understanding of the mechanisms controlling lung extravascular water volume. Although the lungs are functionally exposed to conditions causing an increase in microvascular filtration, such as capillary recruitment, increase in cardiac output and hypoxia, a common condition in cardiopulmonary disorders, the extracellular matrix normally limits extravascular water volume to <10% (interstitial oedema) [1]. Matrix proteoglycans ensure low permeability of capillary endothelium and a fairly rigid interstitial matrix due to their assembly as link molecules within the matrix and among cells [1]. However, a sustained condition of interstitial oedema, as well as lung overdistension, produces severe pulmonary complications, such as acute respiratory distress syndrome, which causes disruption of the extracellular matrix leading to an increase in microvascular permeability and unopposed fluid extravasation [1, 2]. Severe oedema results when the process of fragmentation exceeds a critical threshold, a pathophysiological process common to all forms of oedema [1]. Respiratory reactance, measured by forced oscillation at 4–5 Hz, decreases progressively as interstitial water accumulates and is an early marker of developing oedema that precedes change in lung compliance or alveolar fluid accumulation [3]. Results of these studies are of interest in pneumology, handling of critical and intensive care from prematurity to adults, and in thoracic surgery. At a more basic level, lung cells have been shown to promptly respond to changes in parenchymal forces by expressing specialised signalling platforms (lipid micro domains) possibly reflecting differential transduction mechanisms tuned to promote specific reparative process [4]. Thus, physiological principles are now being applied at a cellular level.

Advances in our understanding of the cellular mechanics and genesis of pulmonary oedema have been important theoretically, but for many clinicians it is the increased availability of integrated exercise physiological testing which has had the most immediate clinical impact. Cardiopulmonary exercise testing (CPET) has proven to be a powerful tool to explain exercise limitation, offer prognostic information and investigate patients with atypical breathlessness. It is no accident that 7% of the papers published in the *European Respiratory Journal* during this 20-yr period have been on exercise-related topics. Exercise testing in chronic obstructive pulmonary disease (COPD) patients has shown that dynamic hyperinflation is common and responsive to bronchodilator treatment [5]. The physiopathological response to exercise has been described for most respiratory conditions [6]. New tests, such as the ''shuttle'' walking test, have appeared [7] while the identification of specific prognostic values of exercise parameters has given a second wind to clinical exercise testing as a prognostic tool [8]. The scope of innovation has been remarkable. On the one hand, new methods of measuring daily activity outside of the laboratory have shown the true extent of how impaired COPD patients actually are [9], while on the other hand cellular [10] and molecular biology allows us to understand the mechanisms of reduced exercise tolerance in many pulmonary conditions [11]. Advances in gas exchange have been led by the limited number of groups with access to the multiple inert gas elimination technique in conditions such as pulmonary hypertension (PH) and hepatic-pulmonary syndrome or asthma. For the first time we can study peripheral oxygen diffusion in males

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with new technologies such as near infrared spectroscopy, as well as report new fractal descriptions of the bronchial tree and their implication in ventilation–perfusion matching using new techniques such us hyperpolarised ^{3}He imaging [12].

The use of novel biophysical measurement techniques has energised physiological research and is well illustrated in the ways these techniques have been applied to common diseases such as COPD and asthma. We now have accurate methods of measuring pulmonary and chest wall mechanics, biochemical, morphological and mechanical assessment of skeletal muscles, and functional imaging. Expiratory flow limitation, a major feature of COPD, can be accurately and noninvasively detected by analysing breath-by-breath variation of respiratory system reactance measured by the forced oscillation technique [13]. Chest wall kinematics, namely total and compartmental chest wall volume variations during rest and exercise, can be measured by opto-electronic plethysmography [14]. Molecular, biological and genetic technologies uncover genotypes predisposing to disease and the molecular mechanisms of alveolar inflammation and striated muscle dysfunction.

Using these different techniques at least three separate mechanisms of exercise limitation in COPD have been described in the last few years [15], including: 1) dynamic hyperinflation leading to an inability to increase tidal volume; 2) skeletal muscle dysfunction resulting from prolonged deconditioning and systemic disease; 3) inadequate energy supplies to meet locomotor and respiratory muscle demands.

With the advent of novel imaging modalities, such as high-resolution computed tomography, magnetic resonance imaging with hyperpolarised gases [16] and optical coherence tomography [17], we can differentiate discrete morphological phenotypes of COPD, namely small airway and parenchymal abnormalities. The challenge now is to understand how these observations relate to more familiar categorisation based on clinical features and treatment responses.

SLEEP-DISORDERED BREATHING

The advent of polysomnography opened up a new world to the pneumologist. While initially research relating to the regulation of ventilation prevailed, later the obesity epidemic reached the pneumologist in the form of obstructive sleep apnoea (OSA). The disease gained wide interest due to the introduction of a simple and effective treatment concept: splinting the upper airway by using continuous positive airway pressure (CPAP). The past 20 yrs have witnessed a tremendous increase in the unravelling of the complex burden of sleep apnoea covering basic aspects such as regulation of ventilation, oxidative stress, inflammation, metabolism, endothelial dysfunction, sympathoexitation and clock gene dysfunction, as well as severe clinical sequel, namely neurocognitive, cardiovascular and socioeconomic [18, 19].

As is similar in COPD, this broad approach brought the pneumologist into close contact with basic research, cardiology, epidemiology, genetics, preventive medicine and the realm of the health system. OSA is now accepted as an independent risk factor for arterial hypertension in authoritative guidelines. Furthermore, recent heart failure guidelines stress the importance of CPAP treatment in documented OSA: class of recommendation 2a, evidence C [20]. Since central and obstructive apnoeas are common in heart failure [21], cardiologists now acknowledge the importance of sleep apnoea in their clinical practice.

Not every patient accepts CPAP and other treatment modalities such as mandibular advancement devices have been successfully tested. As a result, the ERS has established a task force on non-CPAP therapies and the recommendations will be published in the near future. A *European Respiratory Monograph* on sleep apnoea will also follow shortly.

Making the right treatment choice depends on our insights into the upper airway physiology. Local therapies are not always successful and predictors, known from larger studies, are not useful in individual patients. Therefore, one needs to explore the upper airway with functional tests such as measurements of the critical closing pressure [22] or sleep endoscopy [23]. More recently, enhanced imaging techniques have been used to study the upper airway volume and regional resistance. Based on these imaging techniques one can also predict the outcome of mandibular advancement devices [24]. The success of novel therapies for OSA interfering with the upper airway geometry and volume will all depend on the accuracy of predicting outcome. This will also be the case when applying electrical stimulation of the nervus hypoglossus. Preliminary studies have shown this technique to have a great potential [25], but clinical studies are still ongoing.

Upper airway interventions are also of great importance in the cure of OSA in children, but the obesity epidemic has also changed the picture of sleep apnoea in children. Distinction between obesity-related sleep apnoea and sleep apnoea due to adenotonsillar hypertrophy will be a challenge in this population [26].

Obstructive and central sleep apnoea highlight the concept of a feedback loop controlling ventilation. This led to renewed interest in adaptive and maladaptive control mechanisms mutually interacting with systemic effects in patients with lung disease.

PULMONARY EMBOLISM AND PH

The annual incidence of venous thromboembolic disease ranges from one to two cases per 1,000 persons and is strongly age dependent, as the incidence rises to nearly 1% per year in those aged >75 yrs. A recent epidemiological study confirmed that venous thromboembolic disease is a major public-health burden with an estimated 370,000 related deaths in 2004 in six European countries. Moreover, pulmonary embolism may lead to persistent chronic disease, *i.e.* CPET, which can be severely disabling [27]. Major advances in the field have been witnessed over recent years, with better use of diagnostic algorithm based on the analysis clinical probability, circulating biomarkers and imaging techniques. In parallel, novel therapies are now available and are developing [28].

PH is a leading source of research and development in cardiopulmonary medicine. A major event in 2009 was the publication of the guidelines for the diagnosis and treatment of PH by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology and the ERS, endorsed by the International Society of Heart and Lung Transplantation [27]. This publication emphasises the strong links between the respiratory and cardiology communities

in this area. The term PH describes a group of devastating and life-limiting diseases, defined by a mean pulmonary artery pressure ($\bar{P}_{pa}$) $\geqslant$25 mmHg at rest, as measured by right heart catheterisation [27]. Recent re-evaluation of the available data has shown that the normal $\bar{P}_{pa}$ at rest is 14 mmHg, with an upper limit of normal of 20 mmHg [29]. Therefore, the significance of a $\bar{P}_{pa}$ between 21–24 mmHg is unclear [27]. Patients presenting with $\bar{P}_{pa}$ in this range need further evaluation in epidemiological studies. Such studies should be a priority for our community. In addition, the definition of PH on exercise as a $\bar{P}_{pa}$ of $\geqslant$30 mmHg as assessed by right heart catheterisation is not supported by published data and healthy individuals can reach much higher values [29]. Thus, no definition for PH on exercise can be provided at the present time, emphasising the need for further studies in the field [27]. Pulmonary arterial hypertension forms group 1 of the new PH classification and is characterised by pre-capillary PH (*i.e.* PH with a normal pulmonary artery wedge pressure $\leqslant$15 mmHg), with a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death [27]. Although we are still far from a cure for pulmonary arterial hypertension, recent advances in the use of targeted therapies have led to improvements in symptoms, exercise capacity and, in some cases, survival [27]. Evidence also suggests that early management may improve outcome [27]. Given such advances, early recognition and prompt and accurate diagnosis of PH and its underlying aetiology are of critical importance before the development of refractory right heart failure [27]. One of the main predictors of death in pulmonary arterial hypertension is reduced right heart function and, therefore, the mechanisms leading to right heart failure and its management are of major interest to our community [30].

Finally, rare variants of difficult-to-manage PH, such as pulmonary veno-occlusive disease, are under recognised and often misdiagnosed [31]. As this condition is recognised as one of the more malignant forms of PH, it is timely to increase awareness of this orphan condition. Indeed, management of pulmonary veno-occlusive disease is complex with a significant risk of severe pulmonary oedema in such patients receiving pulmonary vasodilators [31]. However, it is timely to review the management of pulmonary veno-occlusive disease in the modern management era: cautious use of pulmonary vasodilators such as continuous intravenous epoprostenol may improve clinical and haemodynamic parameters in patients displaying pulmonary veno-occlusive disease without commonly causing pulmonary oedema, and may be a useful bridge to urgent lung transplantation [31, 32].

AN AFTERWORD

As this brief summary reveals, the scale and speed of progress in both clinical and basic respiratory physiology has been terrific in the last 20 yrs. There is no sign that this momentum is diminishing. On the contrary, new ideas, applications and observations are coming thick and fast and are being quickly translated into new diagnostic and treatment options for patients. It does seem that reports of the death of physiology have been premature!

STATEMENT OF INTEREST

Statements of interest for S. Andreas and M. Humbert can be found at www.erj.ersjournals.com/misc/statements.dtl

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