Bridging the gap in knowledge between dyspnoea scientists and clinicians

Dan Adler¹,²

Affiliations: ¹Division of Pulmonary Diseases, Geneva University Hospitals, Geneva, Switzerland. ²Dept of Internal Medicine Specialties, Geneva Medical School, Geneva, Switzerland.

Correspondence: Dan Adler, Division of Pulmonary Diseases, Geneva University Hospitals, 4–6 Rue Gabrielle-Perret-Gentil, 1211 Geneva 14, Switzerland. E-mail: dan.adler@hcuge.ch

A study in the ERJ suggests that dyspnoea per se is a major clinical endpoint in a chain of events leading to physical disability http://ow.ly/QGEg30l6gfj

Cite this article as: Adler D. Bridging the gap in knowledge between dyspnoea scientists and clinicians. Eur Respir J 2018; 52: 1801308 [https://doi.org/10.1183/13993003.01308-2018].

Dyspnoea can be defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” [1]. It derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses. The current definition of dyspnoea highlights the importance of the multidimensional nature of dyspnoea (sensory–perceptual, affective distress and impact domains), which in turn has led to the development of multidimensional tools to assess dyspnoea [2, 3]. Our current understanding of dyspnoea has been fostered by the ongoing efforts of a community of scientists focused on the multidisciplinary/translational aspects of dyspnoea research. As a result of continuous education, in which the European Respiratory Society was also involved, clinicians caring for these patients in daily practice finally agreed that dyspnoea is a neutral word to “hide” major respiratory suffering in individual patients [4]. Indeed, chronic breathlessness is very often compared with chronic pain and shares many neurophysiological similarities [5, 6].

Translational research suggests that when pathophysiological factors related to lung disease have been corrected, novel therapeutic approaches related to the brain integration of afferent information and the affective impact of dyspnoea may be a worthwhile path of study [7, 8]. For instance, the concept of dyspnoea–pain counterirritation, defined as the attenuation of pre-existing pain by intercurrent, experimentally induced dyspnoea, has well established neurophysiological correlates. By expanding the very same concept from the bench to the bedside, DANGERS et al. [9] were able to demonstrate that relieving dyspnoea by noninvasive ventilation in patients with amyotrophic lateral sclerosis (ALS) was associated with decreased pain thresholds. This observation suggests that patients with ALS may become more susceptible to pain after initiation of noninvasive ventilation. A benefit on both dyspnoea and pain can also be achieved with pharmacological treatment targeting central opioid receptors. Currently, administration of low-dose opioids is the only evidence-based treatment to reduce chronic breathlessness [10]. Finally, by analogy with a recent approach in pain research, the modulation of breathing perception through virtual reality seems to be a new and promising research avenue [11, 12].

By contrast, classical clinical research has mainly focused on treating underlying pathophysiological dysfunction as the target of an intervention, rather than dyspnoea itself. This has met with conflicting results as most underlying pathological processes, such as emphysema or fibrosis, are not reversible. Why scant attention has been given to dyspnoea itself in clinical research is surprising, since it is a point of convergence for and the final path of most chronic respiratory diseases. However, evidence that dyspnoea
is a major clinical endpoint remains scarce, although it has been shown to be an important predictor of
mortality in the general population [13] and is a frequent symptom in all hospitalised patients [14].
Moreover, dyspnoea is a better predictor of mortality than forced expiratory volume in 1 s in patients with
chronic obstructive pulmonary disease (COPD) [15]. Recent evidence also suggests that dyspnoea is an
independent predictor of readmission or death in a selected group of COPD patients surviving respiratory
failure, even after multiple adjustments for major comorbidities [16]. Thus, a robust demonstration that
dyspnoea per se has a major impact on clinical outcome was needed to bridge this gap of knowledge
between dyspnoea scientists and clinicians.

The important study by RAMON et al. [17] in this issue of the European Respiratory Journal (ERJ) has taken
up the challenge of putting together “expert opinion” on the widely accepted concept of the dyspnoea–
inactivity vicious circle and real-world data obtained from two international, large-scale COPD cohorts
(PAC-COPD [18] and ICE COLD ERIC [19]). First, they identified nine previously published conceptual
models of the dyspnoea–inactivity vicious circle based on expert opinion. Using fitted equation models, the
authors were able to demonstrate that none of the current models showed an appropriate fit with real-world
data, although all of them replicated known associations between variables selected for the dyspnoea–
inactivity vicious circle. Second, they developed a comprehensive new vicious circle model using a limited
number of candidate variables from the PAC-COPD cohort by the inclusion of biologically plausible variables
and the stepwise exclusion of variables that did not improve model fit. Third, they validated the new model in
the ICE COLD ERIC cohort to ascertain generalizability of the model in a second COPD cohort.

RAMON et al. [17] should be congratulated for this report, which is of major importance and will certainly
stimulate the COPD community to design new/early interventions targeting dyspnoea as a specific
endpoint in order to break the vicious circle. As always, there are some limitations but these are
adequately addressed in the discussion section of the paper. The relatively short follow-up period of both
cohorts may have restricted the ability to identify important variables (such as age) related to the vicious
circle. Another limitation of the study is the use of the modified Medical Research Council (mMRC) scale
to assess dyspnoea. Although the mMRC and the New York Heart Association share the same construct
and are commonly accepted measures of dyspnoea, both tools are in fact measures of disability related to
dyspnoea and not measures of dyspnoea itself [20]. This makes the argument of an association between
dyspnoea and physical activity a bit circular. Therefore, the selection of specific tools to assess dyspnoea
will be a necessary step for further research in the field. It is also unfortunate that “airway obstruction”,
rather than “dyspnoea”, was the entry criterion in the dyspnoea–inactivity vicious circle. Having
“dyspnoea” first in the circle would have increased the scope of the study to other important groups of
patients: 1) symptomatic current or former smokers with preserved pulmonary function [21, 22];
2) COPD and non-COPD patients with multimorbidity [23, 24]; and 3) frail older patients with
respiratory and nonrespiratory diseases [25]. However, the authors clearly state that the study population
was restricted to COPD patients and therefore, their results cannot be generalised to patients with other
chronic respiratory diseases. Lastly, patients lost to follow-up may have had an impact on the selection of
important variables in the final dyspnoea–inactivity model, given that they had a worse functional status at
baseline and were those who died during follow-up. The authors argue that from a clinical point of view,
only patients who survive COPD without severe comorbidities are those who present at clinical practice
with features of the vicious circle.

However, with those limitations in mind, the study by RAMON et al. [17] has the major merit of bridging
an important gap in our knowledge by identifying dyspnoea as a major clinical endpoint in a chain of
events leading to major disability. The ERJ has already demonstrated its commitment in supporting
high-quality, multidisciplinary, translational research [26–28], of which this study is a fine example that
will serve to stimulate clinicians and researchers to design and test novel approaches targeting dyspnoea in
order to change patients’ health trajectories.

Conflict of interest: None declared.

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