



## REVIEW

# Therapeutic implications of the pathophysiology of COPD

P.T. Macklem

**ABSTRACT:** This review examines 18 studies published  $\geq 30$  yrs ago. They show that the earliest manifestation of chronic obstructive pulmonary disease (COPD) is an increase in residual volume suggesting that the natural history of COPD is a progressive increase in gas trapping with a decreasing vital capacity (VC). The reduction in VC forces the forced expiratory volume in 1 s to decline with it. This is aggravated by rapid shallow breathing leading to dynamic hyperinflation. The earlier studies show that this is energetically opposite to a minimal work or force pattern and is responsible for dyspnoea and exercise limitation.

This information, available for  $>30$  yrs leads to three virtually untested hypotheses: 1) training patients to breathe slowly and deeply transiently during exercise should decrease the work of breathing, dynamic hyperinflation and improve exercise performance; 2) rapid shallow breathing is caused by alveolar and bronchial inflammation that stimulates non-myelinated vagal C-fibre afferents, which are known to cause this breathing pattern; and 3) if so, therapeutic efforts to block these afferents might restore a slow-deep pattern and be beneficial, particularly in COPD exacerbations.

**KEYWORDS:** Emphysema, gas trapping, pulmonary C-fibre afferents, rapid shallow breathing

In this era of molecular, cellular and genetic medicine many old contributions to the pathophysiology of respiratory disease are being forgotten and no longer taught. The purpose of this paper is to review valuable old knowledge, not often mentioned nowadays, in order to develop new ideas about natural history, pathophysiology and treatment of chronic obstructive pulmonary disease (COPD). The definition of “old” is published  $\geq 30$  yrs ago. These references are identified in the text and reference list by an asterisk (\*), of the 18 “old” references Jere Mead was an author on six, two more than any other author and five more than most. He was my mentor in 1964–66 and if I have accomplished anything, it is primarily because I had the good fortune to be inspired by his creativity, his commitment to excellence and his ability to stimulate critical thinking. We had serious arguments but they never descended into quarrels. He was a most treasured friend and I dedicate this article, in memoriam, to him (fig. 1). I start with the natural history of COPD.

### THE NATURAL HISTORY OF COPD

32 yrs ago FLETCHER and PETO [1\*] pointed out that in COPD there is a progressive, gradually

accelerating decline in forced expiratory volume in 1 s (FEV<sub>1</sub>). This has been universally accepted as the paradigm for its natural history. What they did not consider was the cause of the decrease in FEV<sub>1</sub>, which occurs because of a reduction in forced vital capacity (FVC; FEV<sub>1</sub> can never exceed FVC) and the FEV<sub>1</sub>/FVC ratio [2]. Both play a role. The FEV<sub>1</sub>/FVC ratio decreases because of loss of lung elastic recoil [3\*, 4\*], a *sine qua non* of emphysema [5\*], and because of obstruction in small airways [3\*, 4\*, 6\*], a *sine qua non* of COPD [6\*]. FVC decreases because gas trapping causes residual volume (RV) to increase more than total lung capacity (TLC).

RV increases due to both loss of elastic recoil and small airways obstruction. All intrapulmonary airways are held open by the radial traction of alveolar walls attached to their outer surface [7\*]. This is particularly important for the bronchioles because it is the only agency which maintains their patency. They are very compliant and without radial traction they would easily collapse. The magnitude of radial traction is approximated by lung elastic recoil pressure [7\*], which decreases with lung volume. At RV, elastic recoil pressure becomes zero and the small

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**FIGURE 1.** Jere Mead doing what he liked most.

airways lose their support and close. With the progressive loss of elastic recoil that characterises emphysema, closure occurs at progressively higher lung volumes [8, 9\*]. This is exacerbated by small airway obstruction, because the narrowed lumen intensifies the effect of surface tension at its air-liquid interface and because the airway smooth muscle shortening necessary to close the airway becomes less.

Indeed it has been known for nearly 50 yrs that an increase in RV is one of the first functional abnormalities in chronic bronchitis [10\*, 11\*]. Thus gas trapping is a primary event. However, it is known that in COPD RV is a dynamic measurement; the longer the expiration the lower the RV. Thus airway closure does not have to be complete, but narrowing must be extreme. In all likelihood RV in early COPD is a combination of airway closure and expiratory flow limitation at low lung volumes, as it is in older healthy subjects [12\*]. Indeed, COSIO *et al* [13\*] found that closing capacity was significantly increased in smokers, although closing volume was not. The addition of RV to closing volume made the difference significant in smokers. CORBIN *et al.* [9\*], in a 4 yr follow-up study found no significant change in FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio, which remained normal in smokers. However, RV, TLC, and the RV/TLC ratio were significantly increased while lung elastic recoil decreased, particularly at high lung volumes, explaining the increase in TLC [9\*]. This increase allowed the vital capacity to remain the same or even increase somewhat. This is why the FEV<sub>1</sub> did not decrease. Clearly, significant pathophysiological changes occur in the early natural history of COPD before any change in FEV<sub>1</sub> and the FEV<sub>1</sub>/FVC ratio.

As the disease progresses and RV increases more than TLC, VC falls and FEV<sub>1</sub> falls with it. The primary event, gas trapping, is a major reason for a progressive decline in FEV<sub>1</sub>. Thus, a strong argument can be made that a change in paradigm is desirable to understand the natural history of COPD.

The new paradigm would emphasise the role of gas trapping, with the decrease in FEV<sub>1</sub> secondary to it as illustrated in the schematic shown in figure 2. This is important because it focuses therapy on allowing trapped gas to escape, rather than

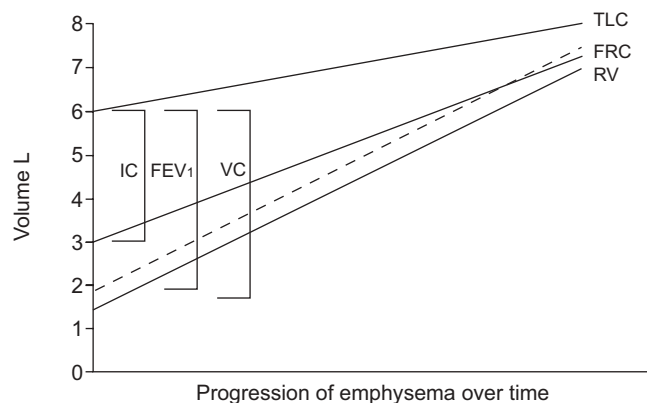
improving FEV<sub>1</sub>. Indeed if trapped gas could escape so that FVC improved, FEV<sub>1</sub> would increase at constant FEV<sub>1</sub>/FVC. But the important therapeutic benefit would result from the decrease in trapped gas reflected in a decrease in RV and RV/TLC ratio; the increase in FEV<sub>1</sub> would be secondary.

A large decrease in trapped gas can be easily achieved in explanted emphysematous lungs removed at transplantation surgery by providing artificial pathways either through the pleural surface or the bronchial wall directly into parenchymal regions of gas trapping allowing trapped gas to escape [14, 15]. Transbronchial fenestration (airway bypass) has become a promising new experimental treatment for emphysema [14] currently being evaluated by a controlled, double-blind, multi-centre clinical trial. Spiracles extending through the chest wall into emphysematous lung tissue has also been performed in patients with substantial benefit reported [16]. But if it were possible to alter the breathing pattern in COPD, many of the ill effects of gas trapping might be avoided.

### THE BREATHING PATTERN IN COPD

When breathing is measured non-invasively [17] there is a wide variation in the way patients with COPD breathe [18, 19]. Some breathe slowly and deeply while most breathe rapidly and shallowly. The rapid shallow breathing pattern is strongly associated with CO<sub>2</sub> retention no matter how ventilation is measured [18–24].

From an energetic point of view, rapid shallow breathing in COPD is diametrically opposite to the pattern resulting in minimal work. Because the lungs in COPD are hypercompliant due to loss of elastic recoil, and the airways are obstructed, a slow deep breathing pattern should result in minimal work. Such a breathing pattern takes advantage of the small pressures required to overcome the elastic recoil of the emphysematous lung, while minimising the pressures required to produce flow through the obstructed airways. This should diminish dyspnoea and improve exercise performance but very few patients breathe this way [18] (unpublished data). Importantly, the faster one breathes in COPD, the less the



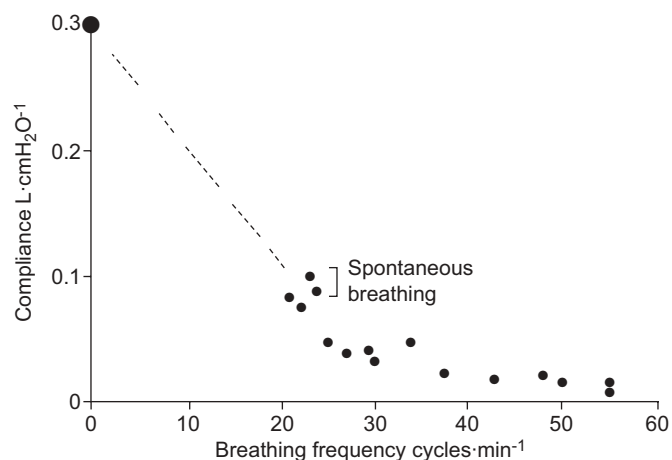
**FIGURE 2.** Schematic illustrating that the natural history of chronic obstructive pulmonary disease is characterised by a progressive increase in gas trapping measured by a progressive increase in residual volume (RV). A lesser increase in total lung capacity (TLC) leads to a progressive decline in vital capacity (VC) imposing a reduction in forced expiratory volume in 1 s (FEV<sub>1</sub>). FRC: functional residual capacity; IC: inspiratory capacity.

dynamic lung compliance becomes [25\*]. As illustrated in figure 3, dynamic compliance during rapid breathing can fall to  $0.05 \text{ L}\cdot\text{cm}^{-1} \text{ H}_2\text{O}$  [25\*], values usually only seen in pathologically stiff lungs. The frequency dependence of compliance leads to a progressive increase of respiratory muscle power output as breathing rate increases; this aggravates dyspnoea and limits exercise performance.

During exercise, expiratory muscles are recruited [26], expiratory flows increase and, in COPD, expiratory flow becomes limited by dynamic compression of intrathoracic airways [27\*]. The effects of flow-limitation on the ventilatory pump have recently been reviewed [28]. They include excessive recruitment of expiratory muscles in a vain attempt to increase expiratory flow [27\*, 29, 30]. The excessive expiratory pressures result from slowing the velocity of shortening of expiratory muscles resulting from flow-limitation and are aggravated by  $\text{CO}_2$  retention [31, 32]. This in turn can decrease cardiac output [33]. The increased  $\text{O}_2$  cost of breathing can become  $>50\%$  of total body  $\text{O}_2$  consumption leading to premature competition between respiratory and locomotor muscles for the available  $\text{O}_2$  supply [34\*, 35, 36]. This was originally pointed out by LEVISON and CHERNIACK [34\*] over 40 yrs ago, in a classic study that has been virtually ignored ever since. Expiratory flow-limitation, by limiting the ability to exhale, forces the patient to breathe at progressively increasing lung volumes severely aggravating the gas trapping and the impairment of lung function that it had already caused. The resulting dynamic hyperinflation further increases the work of breathing and intensifies dyspnoea dramatically when the inspiratory reserve volume approaches zero [37, 38].

Clearly, rapid shallow breathing is a disastrous way for patients with COPD to breathe. All the functional abnormalities described above result directly from this breathing pattern or are aggravated by it. Its pathophysiological effects explain why COPD turns its victims into respiratory cripples imprisoned by dyspnoea, severe exercise limitation and inability to carry out routine tasks of daily living.

All of these devastating manifestations should be ameliorated if patients breathed slowly and deeply. Is this possible?



**FIGURE 3.** Lung compliance as a function of respiratory frequency in an emphysema patient. Reproduced from [22] with permission from the publisher.

## THERAPEUTIC IMPLICATIONS

The respiratory muscles are the only skeletal muscles under both brainstem and cortical control. If this were not so, speaking would be difficult and eating, life-threatening. When we are not thinking about how we breathe, our respiratory muscles are under the control of the brainstem respiratory centres. However, we can voluntarily breathe any way we want by bringing breathing under cortical control. Hence it is possible for patients with COPD to breathe slowly and deeply, and a few of them naturally breathe that way [18]. But others with faster respiratory rates have to think about their breathing in order to have cortical control to breathe slowly and deeply. It is unlikely that ventilation can be maintained this way during all the waking hours and certainly not during sleep; however, it might be possible to exert cortical control and initiate a slow deep breathing pattern transiently during exercise and other activities limited by dyspnoea. Physiotherapy in COPD has rarely focused on such a breathing pattern. A PubMed search yielded only two hits [39, 40] for “slow deep breathing, physiotherapy and chronic obstructive pulmonary disease” and only one [39] dealing with chronic lung disease for the key words “slow deep breathing, physiotherapy, exercise”. This paper pointed out that teaching patients to breathe slowly and deeply provided temporary benefits, which is precisely the aim in patients with COPD during exercise. A physiotherapeutic trial to teach COPD patients to breathe slowly and deeply during exercise must be undertaken to test this hypothesis.

When external loads are applied to the respiratory system a breathing pattern results that minimises the work or force of breathing [41\*–44\*]. So why do patients with COPD breathe in a way that aggravates the obstruction and creates an artificial elastic load? Non-myelinated bronchial and/or alveolar vagal C-fibre afferents might be the culprit. Indeed it would be surprising if these afferents were not stimulated in COPD. Alveolar and/or airway inflammation, characteristic features of emphysema [45, 46], stimulate these fibres which cause rapid shallow breathing, increased airway secretions and bronchoconstriction [47–49], all of which are prominent features of COPD. In experimental animals, C-fibre afferent stimulation causes muscle weakness [49], but whether this plays an aetiologic role in the skeletal myopathy of COPD [50] has not been investigated. These fibres are also stimulated by a transient respiratory acidosis [51]. If this is the case in COPD a mild upper respiratory inflammatory reaction could be responsible for almost all the features of an acute exacerbation including increased airways obstruction, mucus hypersecretion, worsening of rapid shallow breathing leading to acute respiratory failure. This could set off a vicious circle in which respiratory acidosis magnified all the effects of C-fibre stimulation leading to increasing hypercapnia and so forth.

It is hardly likely that C-fibre stimulation, which reproduces so many features of COPD is merely a coincidence. A reasonable hypothesis can surely be made that afferent C-fibre stimulation by inflamed alveoli and airways in COPD plays an important role in excessive mucus secretion, airways obstruction, the rapid shallow breathing pattern, skeletal myopathy and  $\text{CO}_2$  retention, particularly during acute exacerbations. In this regard, it is interesting that local anaesthesia of the airways



in COPD changes the breathing pattern to a slower deeper one [52].

The role of C-fibre afferents in COPD is apparently an uninvestigated question. A PubMed search turned up no references suggesting that COPD stimulates vagal C-fibres. However, the evidence quoted above strongly indicates the need for such research.

Could this be treated by intravenous infusion of a local anaesthetic? This would have to be tested in an animal model before trying in humans. However, if it worked it should restore a slow deep pattern that should improve dyspnoea and exercise performance while decreasing dynamic hyperinflation. It might also be an effective treatment of acute exacerbations.

## CONCLUSIONS

Old important publications should not be forgotten. Even after many years they may still point to untried therapeutic endeavours. This is not true just for the older articles I have quoted. There are many classic old studies in the field of respirology that are still highly pertinent.

By reviewing old literature about loss of elastic recoil [5\*] and peripheral airways obstruction [6\*] in COPD and how these lead to expiratory flow limitation [3\*, 4\*] the concept emerges that when this occurs in COPD the work of breathing can become excessive and lead to severe dyspnoea and impaired exercise performance [27\*, 34\*]. Furthermore the loss of recoil and airways obstruction lead to gas trapping [9\*, 13\*] manifested by an increase in RV before there is any significant change in FEV<sub>1</sub> [9\*–11\*, 13\*]. This suggests that the natural history of COPD as a progressively accelerating fall in FEV<sub>1</sub> [1\*] needs to be changed to focus on gas trapping as the primary event with progressively increasing amounts of trapped gas as the major feature of COPD's natural history.

The normal response to breathing with increased loads is to minimise work or force [41\*–44\*]. This does not happen in most patients with COPD who breathe rapidly and shallowly, markedly increasing both the elastic and flow-resistive work of breathing [25\*], a pattern diametrically opposite to the normal response.

These important old papers not only suggest that we need a new paradigm for the natural history of COPD, but also suggest three hypotheses: 1) physiotherapeutic programmes to teach patients with COPD to breathe slowly and deeply during transient periods of exercise should lessen dyspnoea and improve performance; 2) many of the pathophysiological manifestations of COPD including most of those that characterise exacerbations are due to stimulation of airway and alveolar vagal C-fibre afferents; and 3) if hypothesis 2) is valid then effective treatment of rapid shallow breathing and exacerbations might be achieved by intravenous administration of local anaesthetics. A literature search does not reveal that these hypotheses arising from the older literature have ever been seriously tested.

## STATEMENT OF INTEREST

A statement of interest for P.T. Macklem can be found at [www.erj.ersjournals.com/misc/statements.dtl](http://www.erj.ersjournals.com/misc/statements.dtl)

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