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Chronic Obstructive Pulmonary Disease Exacerbations: Accurate and Easy Measurement Promises Much

> An experiment is a question which science poses to Nature, and a measurement is the recording of Nature's answer.
> —Max Planck, *Scientific Autobiography and Other Papers*

By definition, acute exacerbations of chronic obstructive pulmonary disease (COPD) are themselves morbid clinical events. However, investigators have also found that the frequency and severity of exacerbations are associated with poor long-term outcomes in patients with COPD, including worsened lung function (1), a decline in health status (2), and mortality (3). Indeed, an important benefit associated with many approved therapies for COPD is a reduction in the frequency of exacerbations (4). Therefore, it is reasonable to expect that improved tools to quantify the frequency and grade the severity of exacerbations of COPD might improve our ability to identify patients at high risk for adverse outcomes and target them for more intensive interventions.

There is consensus on the treatment of acute exacerbations (4) with a combination of therapies including bronchodilators, systemic glucocorticoids, and antibiotics. The use of short-acting bronchodilators is a mainstay of therapy; however, there have been no randomized trials demonstrating their efficacy, in part because such trials would be difficult to design in an ethical manner. Therefore, the evidence for this recommendation was graded level C in the most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (4). Systemic glucocorticoids have been demonstrated in randomized clinical trials to improve lung function, reduce hypoxemia, and reduce treatment failures, and are therefore recommended with an evidence grade level A. Antibiotics are recommended at evidence level B for all patients in whom all three cardinal symptoms—cough, sputum, and dyspnea—are present, and in patients who require mechanical ventilation. If only two symptoms are present, antibiotics are recommended with evidence graded at level C. Apart from general support and addressing comorbidities, no other therapies are recommended in the GOLD guidelines. Clearly, well-designed trials of novel or existing therapies in patients with COPD exacerbations focused on both short- and long-term outcomes are needed to improve therapy for COPD. Such trials are hampered by our limited ability to measure exacerbation frequency and severity. The article by Mackay and colleagues in this issue of the *Journal* (pp. 1218–1224) provides a new tool, the COPD Assessment Test (CAT), that may address this limitation (5).

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The CAT is a self-administered questionnaire developed with rigorous psychometric techniques to generate a severity score from self-reported COPD symptoms (6, 7). Because its measurement properties were developed to allow statistical comparisons, it is well suited for use in clinical trials. Mackay and coworkers used the CAT to assess exacerbation severity in a well-characterized prospective cohort of COPD patients in London. In that cohort, they found that the CAT increased with exacerbations. More importantly, the magnitude of the CAT increase was directly related to the decline in lung function during the exacerbation, the duration of the exacerbation as determined by symptom scores, and the change in C-reactive protein (CRP). The investigators were able to show that within the group of patients with moderate exacerbations, event severity can be further quantified and related to clinical endpoints. Importantly, event severity was not related to baseline comorbidity, suggesting that the CAT measures the severity of the event, not baseline severity of disease.

The CAT provides an important advance over the most common current method to assess COPD severity using health care utilization (8). According to these criteria, a self-managed event is mild, an outpatient-managed event is moderate, and an event requiring hospitalization is severe. While this measure has important advantages, it is confounded by baseline health care status—individuals with very severe disease are much more likely to be hospitalized. The CAT appears to overcome this limitation; however, all the subjects included in the Mackay study would be classified according to these criteria as having "moderate" exacerbations. How the CAT will perform for patients who would be "mild" and "severe" according to the health care utilization criteria is an important, yet unanswered question.

There are limitations to these relationships that will attract the attention of many "naysayers." The CAT is a single number, which collapses several distinct measures of disease activity into a single variable. The CAT, therefore, does not reflect the heterogeneity of COPD, only its severity. In addition, the relationships with lung function ($r = 0.20$) and with CRP ($r = 0.26$) are weak and the relationship with exacerbation duration is a bit circular, because the CAT is largely based on symptoms, which were used to define duration. Furthermore, the London cohort completed diary cards daily. Although all events were assessed and confirmed by study staff, data from these diary cards were used to define exacerbation events. It is therefore impossible to exclude the possibility that the diary cards cued the subjects to seek health care.

It is important to recognize that the CAT was *not* evaluated as a diagnostic test for a COPD exacerbation in the Mackay article. In fact, several of the subjects had a decline in their CAT score with exacerbation, and several more had no change. These would represent "false negatives" if CAT were used diagnostically to define events. Similarly, it is not known what changes occur in the CAT when there is no exacerbation. Thus, a false-positive rate cannot be estimated. Similarly, it is not known how other acute conditions with symptoms similar to COPD exacerbations, for example, congestive heart failure, might reduce the specificity of the CAT.

Finally, there may be better tests than the CAT to assess COPD exacerbation severity. The EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) was developed with rigorous psychometric methods specifically to define events permitting rigorous assessment of COPD exacerbations (9–11). It has measurement characteristics that make it suitable as a gauge of severity. EXACT requires repeated measures over a period of time to establish both baseline status and exacerbation events, which may complicate its use for some clinical investigators. EXACT is currently under review with the United States Food and Drug Administration (FDA) and European Medicines Agency to determine if it will be qualified for the assessment of exacerbations for use in drug development. If approved, it will provide a measure that drug developers can use with confidence. The CAT is not currently being reviewed in this capacity. Whether the CAT will be accepted for this purpose will depend on the acquisition of a robust dataset that demonstrates its utility and a sponsor willing to prepare a dossier for FDA review. Finally, how these patient-reported outcomes will compare with biochemical measures that increase with exacerbation as gauges of severity remains to be determined (12).

So, with these limitations, why is the Mackay article so important? It is because it gives us another tool that can be easily applied by the clinical investigator to measure the severity of COPD exacerbations. This methodology provides a means to address crucial clinical questions such as the following: Is the impact of exacerbation on FEV_1 decline, subsequent mortality, or impact on health status related to event severity? Do treatments reduce severity of exacerbations in addition to reducing their frequency? Does reduction in exacerbation severity have an impact on disease progression? These questions are of paramount importance to clinicians and patients alike and absolutely require an adequate tool to measure exacerbation severity. The demonstration that this is possible promises an explosion of understanding of COPD exacerbations.

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The Role of the Inflammasome in Ventilator-induced Lung Injury

The immune system has a number of ways to respond to external threats. Invading pathogens and danger signals are recognized by different pattern recognition receptors (PRRs), which may be either on the membrane surface (e.g., Toll-like receptors) or inside the cytoplasm (e.g., Nod-like receptors [NLRs]). In 2002, Martinon et al. (1) described a novel subset of NLRs that were able to assemble and oligomerize into a common structure that collectively activated the caspase-1 cascade, thereby leading to the production of proinflammatory cytokines interleukin (IL)-1β and IL-18. This multimolecular complex was called the "inflammasome." Since then, four distinct inflammasome complexes, defined by the NLR serving as the recognition site, NLR family, pyrin domain containing (NLRP)1, NLRP3, NLR family CARD domain–containing protein 4 (NLRC4), and absent in melanoma 2 (AIM2), have been described (2). Once activated, the inflammasome regulates and executes a variety of immune-related functions—although the nature of the physiological cues that trigger inflammasome activation remains incompletely understood. The strong association between human heritable and acquired inflammatory diseases and dysregulated inflammasome activity has suggested its role in immunity (3). In addition, these same receptors recognize endogenous danger signals, including those arising during metabolic and/or mitochondrial dysfunction, raising the potential importance of this pathway in critical illness (4), especially conditions such as ventilator-induced lung injury (VILI) characterized by hyperinflammation and immune dysregulation.

In this issue of the *Journal*, Dolinay and colleagues (pp. 1225–1234) demonstrated both a mechanistic relationship between VILI and the inflammasome pathway, and the clinical utility of measuring IL-18 in patients at risk for or with acute respiratory distress syndrome (ARDS) (5). The initial evidence implicating the inflammasome pathway in VILI originated in a retrospective analysis of microarray data generated from whole *ex vivo* lungs exposed to experimental VILI and subsequently confirmed prospectively using an *in vivo* mouse model. Differential transcription and protein levels of inflammasome-related caspase 1 (CASP1), IL-18, and IL1β was validated in whole blood from four independent cohorts of critically ill patients and demonstrated a strong association between IL-18 protein levels, ARDS risk, and indices of morbidity and mortality. Having established the clinical significance of the *in silico* hypothesis, the authors closed the mechanistic loop by returning to the bench to show that mice with targeted deletions of either the CASP1 or IL-18 genes, or treated with an IL-18–neutralizing antibody, were protected from VILI. The major strength of the article is the translational biology approach (*in silico*, to bench, to bedside, and back to bench) combined with the human validation strategy.

ARDS, characterized by severe acute inflammation, loss of alveolar–capillary membrane permeability and neutrophilic alveolitis, is a significant cause of morbidity and mortality (6, 7). The need for mechanical ventilation exposes patients to further injury by repetitive cyclic stretch and/or overinflation (8). Although ventilation with small tidal volumes improves mortality (9), most pharmacological treatment approaches have failed in patients (perhaps with the exception of paralytic agents). There are many reasons why "candidate targets for therapy" have not translated into effective treatments. One of the most important reasons is likely our incomplete understanding of the pathogenesis of ARDS/VILI. This is at least in part due to the difficulty in extrapolating data from cell and animal models to humans. The study by Dolinay and colleagues is particularly provocative in that it illustrates the strength of a combined genomic and broad translational approach to biomarker and target discovery, and provides a strong rationale for pharmacological and/or genetic modulation of the newly identified inflammasome pathway in ARDS/VILI.

The different NLRs allow the host to detect a variety of distinct intracellular pathogens and danger signals. Although NLRP3 responds to a plethora of agonists, other inflammasomes appear to have a more narrow recognition spectrum that may not be immediately relevant to VILI (10, 11). Importantly, in many cases, a direct interaction between an NLR and a specific PAMP or DAMP (pathogen- or damage-associated molecular patterns) has not been demonstrated. It is possible that inflammasome activation is directly related to "force-induced" membrane disruption and/or cellular deformation (mechanotransduction). However, none of the components of the inflammasome have been shown to be responsive to mechanical stretch or contain stretch-response *cis*-regulatory elements (yet). A more plausible explanation is that injurious mechanical force(s) activate inflammasome(s) indirectly, as a consequence of *biotrauma* (12) (Figure 1). Mechanical forces likely act by exposing pattern and/or damage recognition receptors to bacterial and/or cellular damage/toxic products generated during (injurious) ventilation. Consequently, in the context of VILI, it may be the ability of the NLRP3 to detect a variety of nonmicrobial danger and mitochondrial stress signals that strongly suggests this inflammasome as the most interesting contributor to pathogenesis (13, 14).

Analogous to Toll-like receptors, the NLRs are thought to function in ligand-binding sensing and autorepression, while the effector domains mediate protein–protein interactions for downstream signaling (4). This is tightly regulated by a variety of endogenous and exogenous feedback loops that may be responsive to cyclic stretch. The role of endogenous and/or pathogen-dependent inhibitors of the inflammasome pathway is of much interest, but very little is known about how they might play a role in modulating inflammation during VILI/ARDS.

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