Is Sustained Pharmacologic Lung Volume Reduction Now Possible in COPD?

International guidelines have correctly highlighted dyspnea alleviation and improvement in exercise tolerance as being among the most important management goals in patients with COPD. Bronchodilator therapy is the first step in achieving these goals, and, in this respect, the advent of therapy with newer long-acting bronchodilators represents a significant clinical advance. Historically, the airflow limitation that characterizes COPD, at least in its later stages, has been thought to be largely “irreversible,” and this may have contributed to a pervasive attitude of therapeutic nihilism. This view has changed, however, and most current consensus documents on the subject acknowledge that the airway obstruction of COPD is indeed “partially reversible.”

Bronchodilator reversibility criteria still rely exclusively on the detection of an arbitrary increase in spirometric maximal expiratory flow rates (i.e., FEV₁). The recognition that bronchodilator therapy can be associated with clinically important improvements in desired patient-centered outcomes such as dyspnea, exercise endurance, and health status, in the presence of little or no change in maximal expiratory flow rates, has prompted a search for additional physiologic markers of improved dynamic airway function. The increase in FEV₁ after therapy with a bronchodilator mainly reflects improved conductance in the larger airways and increased expired flow rates in alveolar units with relatively fast time constants for emptying. Improvements in small airway function after bronchodilator therapy are more difficult to measure, but reduced lung volumes as a consequence of enhanced gas emptying in alveolar units with slower time constants provide us with indirect evidence of a positive effect. Studies have shown that substantial reductions in lung hyperinflation can occur after short-term treatment with short-acting and long-acting bronchodilators in the presence of only modest improvements in FEV₁. Patients who show expiratory flow limitation during spontaneous resting breathing and those with the most severe resting lung hyperinflation have demonstrated the greatest acute lung volume reduction with bronchodilator therapy. Moreover, reductions in lung hyperinflation have been shown to correlate better with improved exertional dyspnea ratings and exercise endurance time than traditional spirometric parameters. These data, together with the known benefits of surgical lung volume reduction, have provided us with a solid physiologic rationale for the clinical benefits of pharmacologic lung volume reduction in COPD patients.

In this issue of CHEST (see page 509), van Noord and colleagues report the effect of combined therapy with long-acting anticholinergic and β₂-agonist bronchodilators on airway function and resting lung hyperinflation over a 24-h period in patients with moderate-to-severe COPD. This study confirmed that the combination therapy of tiotropium every day and formoterol twice a day was associated with an average increase in FEV₁ (0 to 24 h) of 0.198 L, which was significantly greater in magnitude than the improvements with therapy using either tiotropium alone or tiotropium and formoterol in combination each taken once daily. This study showed that combined bronchodilator treatment improves, but does not abolish, this nocturnal worsening of expiratory airway obstruction and lung hyperinflation. The average increase in IC (0 to 24 h) was 0.215 L, with an impressive peak effect within 2 h of dosing of 0.552 L and an average increase of 0.294 L during waking hours (0 to 12 h). Improvements of this magnitude are arguably clinically important and should translate into an important reduction in activity-related dyspnea and an increase in exercise endurance.

In patients with COPD, the smaller the resting IC, the closer that tidal volume is positioned to total lung
capacity and the upper noncompliant extreme of the respiratory systems pressure volume relationship where there is increased elastic loading of the inspiratory muscles. Small increases in IC after bronchodilator therapy, which signify a reduction in end-expiratory lung volume, are associated with reduced mechanical loading and increased functional strength of the inspiratory muscles, resulting in a reduced work and oxygen cost of breathing. Furthermore, an increased resting IC (on the order of 0.3 L or 10% predicted) means a greater ability to expand tidal volume during exercise with a resultant increase in ventilatory capacity. Reduced operating lung volumes during exercise enhance neuromechanical coupling of the respiratory system (ie, the relation between neural drive and mechanical response), thereby relieving respiratory discomfort. The net effect of all of these physiologic benefits is to improve the patients' capacity to engage in exercise. This study raises a number of questions. To the extent that the peak lung deflation achievable with therapy with combined long-acting bronchodilators in this study exceeded 0.5 L, is it possible (or clinically advantageous) to sustain this maximal level over 24 h by using additional bronchodilators or possibly inhaled corticosteroids? What are the mechanisms of this circadian variation, which persists despite effective anticholinergic therapy? Would abolition of the nocturnal dip in airway function result in improved sleep quality and daytime function in COPD patients?

The most intriguing question, in my view, is whether maximal sustained bronchodilation in COPD patients results in positive long-term effects? It now appears that we have the capability of achieving lung volume reduction by pharmacologic means that is comparable in magnitude to that obtained by lung volume reduction surgery. Can we expect a similar survival advantage, and if so, will this be confined to specific subsets of patients? Specifically, do health status and survival improve in response to therapy with combined long-acting bronchodilators in patients with severe COPD and diffuse homogeneous emphysema in whom lung volume reduction surgery is contraindicated?

To date, therapy with long-acting bronchodilators has been studied in relative isolation but has nevertheless shown consistent improvements in airway function and hyperinflation, dyspnea, exercise capacity, the number and severity of exacerbations, and overall health status compared with placebo. The results of the study by van Noord and colleagues lend support to the hypothesis that combined long-acting bronchodilator therapies will have a greater impact on measures of impairment, disability, and handicap than has previously been reported in clinical trials of single bronchodilators. Since each of the above-listed outcome parameters are independent predictors of survival in COPD patients, it is tempting to speculate that modern pharmacotherapy will, in an unprecedented manner, positively influence the natural history of this devastating disease.

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Sputum Induction in Asthma
A Research Technique or a Clinical Tool?

Clinicians have been interested in the study of sputum in asthma patients since the end of the 19th century when Curshman spirals and Charcot-Leyden crystals were first described as being associated with sputum eosinophilia. However, sputum analysis was initially hampered as an investigative tool by a lack of standardization and the inability to obtain a sample in many cases. In the last 15 to 20 years, this problem has been overcome by inducing sputum using hypertonic saline solution, a technique that is safe and reproducible. Good-quality cytospins can be routinely obtained, and a reliable differential cell count can be generated.1

The increasing application of this technique has led to the recognition that inflammation in asthma patients is more heterogeneous than was previously thought with the identification of noneosinophilic asthma.2–4 This phenotype is common, accounting for 25 to 55% of patients with corticosteroid-naive asthma, and is repeatable, with few subjects with noneosinophilic asthma developing airway eosinophilia during follow-up for 1 year.5 This asthma phenotype is not reserved to patients with severe asthma, nor is it a consequence of asthma therapy, but it is present across the range of asthma severity.4 Its identification is important as it is related to a poor response to corticosteroids.2 This view is supported by a study reported in this edition of CHEST (see page 565) by Bacci et al,6 who studied a group of 67 symptomatic asthmatic patients before and 2 and 4 weeks after receiving therapy with inhaled beclomethasone dipropionate, 500 µg twice daily. A total of 17 patients (25%) had noneosinophilic asthma. Consistent with previous studies,2,7 they found that a sputum eosinophil count, but not other markers of inflammation in sputum or peripheral blood, correlated with changes in lung function after corticosteroid treatment. One shortcoming of this study was its open-label design. However, in support of the findings of Bacci et al,6 a placebo-controlled cross-over trial7 of inhaled mometasone, 400 µg once daily for 8 weeks, in subjects who were characterized as having either eosinophilic or noneosinophilic asthma prior to study entry confirmed that a favorable response to corticosteroids is reserved for asthmatic patients with sputum eosinophilia.

In addition to asthma phenotype, smoking status has also been proposed to influence corticosteroid responsiveness in asthma. A series of reports from Glasgow (see the review by Thomson and Spears9) has suggested that smoking confers a relative corticosteroid resistance. However, work from the same group10 found that asthmatic patients who smoked did not have sputum eosinophilia. The study by Bacci et al6 included ex-smokers and current smokers. They found that smoking status per se was not associated with a poor response to corticosteroids, but that in subjects who smoked the presence or absence of sputum eosinophilia remained the best predictor of the response to treatment with corticosteroids. This observation is important as it suggests that the poor response to corticosteroids reported in asthmatic patients who smoke might reflect an absence of a corticosteroid-responsive pathology.

Importantly, the value of measuring airway inflammation in sputum extends beyond these relatively short-term studies on corticosteroid responsiveness. In a randomized placebo-controlled trial,5 74 subjects with asthma were assigned to either a management strategy aimed at normalizing their sputum eosinophil count or standard clinical care. Patients in the sputum management group experienced significantly fewer severe asthma exacerbations than patients in the control group (35 vs 109 patients, respectively; p = 0.01) and significantly fewer patients were admitted to the hospital with asthma (1 vs 6 patients, respectively; p = 0.047). There were no significant differences in the average daily dose of inhaled or oral corticosteroids between the two groups. A reduction in the number of exacerbations was achieved without an increase in the total corticosteroid dose in the sputum guidelines group, as
monitoring airway inflammation in the sputum guidelines group identified a group of patients with non eosinophilic asthma whose sputum eosinophil count remained within the normal range. In these subjects, the dose of corticosteroids was reduced without evidence of deterioration in the control of asthma.

Economic analysis shows that the health-care-related savings occurring as a consequence of the reduction in the number of asthma exacerbations outweighs the cost of sputum induction and processing. This supports a role for this test to be routine in specialist centers. However, sputum induction is labor-intensive and requires laboratory support. Thus, for these reasons it is unlikely that this method could be extrapolated to a primary care setting. Thus, there is a need for a simpler method to identify sputum eosinophilia. Alternatively, the assessment of exhaled gases, such as exhaled nitric oxide, provides a simple measure that can be undertaken in the primary care setting. However, asthma management strategies that use the measurement of exhaled nitric oxide to guide treatment with corticosteroids have not been able to alter exacerbation rates.

In conclusion, the measurement of a sputum eosinophil count has value in predicting the response to corticosteroids, and the regular monitoring of airway inflammation is an important facet of optimal asthma management. Therefore, sputum induction as a useful research technique is not in doubt, but its potential role in the clinic is yet to be realized.

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Endoscopic Lung Volume Reduction Surgery

Cart Before the Horse?

COPD is a significant and growing challenge in the United States and throughout the world. It is difficult to interpret prevalence data, primarily due to varying definitions of COPD. It has been estimated that 2 to 10 million patients in the United States have the disease. COPD is currently the fourth-leading cause of death in the United States; and, in 2000, the World Health Organization reported there were 2.74 million deaths worldwide due to COPD. The human and economic impact of COPD is staggering. Patients with severe disease are often disabled, relying on family members and other caretakers for assistance with activities of daily living. These patients report quality-of-life scores on par with patients with AIDS and terminal cancer. It is estimated that the direct and indirect costs of COPD total $36.1 billion annually in the United States. Despite advances in care, treatment of COPD remains supportive and we are often unable to alter a relentless progression of disease.

In the 1950s, Brantigan and Mueller sought to
relieve dyspnea in their COPD patients by correcting the overinflation of the chest by surgically removing lung tissue. Approximately 75% of patients having “reduction pneumoplasty” reported relief of symptoms of dyspnea. While these investigators were praised for their innovation, they were criticized for the lack of an objective means of determining improvement and an 18% perioperative mortality rate. Widespread enthusiasm for the volume reduction concept was kindled by Cooper and Patterson in the 1990s, who modified Brantigan’s surgical technique and reported very favorable results with an acceptable rate of morbidity and mortality. Hospitals around the United States began performing lung volume reduction surgery (LVRS) with varied results, including an overall perioperative mortality rate approaching 17%. In 1995, after an Agency for Healthcare Research and Quality investigation of LVRS concluded that there was no clear benefit to patients, the Healthcare Financing Administration announced that Medicare would not pay for LVRS. The ensuing political firestorm lead to the creation of the National Emphysema Treatment Trial (NETT), a multicenter, randomized, controlled trial comparing LVRS to medical therapy. The results from the NETT were mixed: while there was no benefit in survival, the surgical patients did have significantly improved exercise capacity and quality-of-life scores. The 90-day mortality rate was 7.9% in the surgical group and 1.3% in the medical group. However, the cost-effectiveness of LVRS therapy was deemed unfavorable. Subgroup analyses from the NETT sought to identify the ideal candidate for LVRS. The significance of NETT subgroup analyses and the proper role of LVRS was, and continues to be, hotly debated. Nevertheless, in 2004, the Centers for Medicare and Medicaid Services announced that Medicare would cover LVRS, performed in approved centers, for the following groups: (1) patients with low exercise capacity and either upper- or lower-lobe predominant disease; and (2) patients with high exercise capacity and upper-lobe disease.

Currently, there is a great deal of interest in new and developing technologies that allow physicians to perform endoscopic LVRS (ELVRS). The devices receiving most attention are endobronchial valves that are placed via a bronchoscope. The valves are placed in targeted lobes with the aim of causing atelectasis, thereby reducing the volume of the thoracic cavity, and restoring a more favorable alignment of the respiratory muscle system. The hope is that patients undergoing ELVRS may achieve all of the benefit that surgical patients in the NETT achieved with very little risk. In this issue of CHEST (see page 518), Wan and colleagues report their experience using endobronchial valves to perform ELVRS in patients with radiographic evidence of heterogeneous disease and persistent dyspnea despite maximal medical therapy. Their study was a multicenter trial, with nine centers participating from seven countries. All patients underwent ELVRS, and the baseline data were employed to determine if ELVRS was beneficial. Study end points included change in FEV1, FVC, residual volume, and exercise tolerance as assessed by a 6-min walk test. Results are reported up to 90 days after ELVRS was performed. The most significant changes were a 10.7% overall improvement in FEV1 and a 23% improvement in exercise capacity. Comparing these results to those of the NETT is difficult for the following reasons: (1) the NETT reported results from 6 months, 12 months, and 24 months; (2) improvements in FEV1 and exercise tolerance decreased over time in the NETT; and (3) NETT results were reported in histograms for patient groups. The NETT, for example, reported that 65% of patients in the surgical group had an improvement in FEV1 6 months after LVRS and that improvement averaged approximately 11%. Wan et al report that 8 of their 98 patients (8.2%) had serious complications: death, n = 1; pneumothorax requiring surgery, n = 3; and prolonged air leak, n = 4. Additionally, the authors observed other complications in 30 patients, including 5 pneumonias and 17 exacerbations of COPD. Finally, the authors performed a subset analysis and noted that patients treated with valves targeting one lobe or valves placed unilaterally achieved better results than the others.

Wan et al deserve accolades for conceiving and performing this investigation. Their study has several merits. First, it is the largest series of ELVRS reported to date. Prior studies have been small, observational series looking at the feasibility of the procedure. Second, the authors chose objective, physiologic outcome measures rather than the more subjective quality-of-life questionnaires as study end points. This increases the impact of their findings. Third, the study demonstrates that ELVRS can be done safely, with an acceptable complication rate, in centers with expertise in pulmonary endoscopy. Finally, it suggests that patients undergoing ELVRS may achieve real and significant improvements in pulmonary function after the procedure.

However, while the observations of Wan et al are intriguing, a few caveats are in order. First, it is very difficult to interpret the results of this study since there was no control group. Indeed, it may be time to change our approach to creating a control group in these studies. In 2002, Moseley et al reported their experience performing arthroscopic debridement, arthroscopic lavage, or a placebo procedure on 165 consecutive patients with osteoarthritis of the knee.
All three groups experienced similar complications and rates of improvement of symptoms, with no procedure demonstrating superiority. Performing a sham endoscopy procedure in an ELVRS study might be the most effective manner to create a meaningful control group. Second, an analysis of subsets in this study to identify the ideal technique or candidates for ELVRS seems premature.

Despite all of its promise, and all of our enthusiasm, we are not yet certain if ELVRS is truly effective. Indeed, a multicenter, randomized, controlled trial of another endobronchial valve for ELVRS is currently underway. Let us await the results of this trial before further efforts are made to identify the ideal candidate, device, or technique for ELVRS.

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Introducing “Medical Writing Tips of the Month”

A New Section in CHEST

“G"iven the importance of medical writing to the progress of civilization, one might expect the art to be widely cultivated and highly perfected. Such is not the case at all. Modern medical literature is some of the most vapid, obscure, tortuous, and unreadable material in print.”1 We would submit that the obtaining of information, especially clinical information, involving as it does the cooperation and rights of patients, carries with it the inherent ethical obligation to communicate the knowledge that can be derived therefrom with maximal impact.

In this issue of CHEST (see page 822),2 we introduce the first article of a new section, entitled “Medical Writing Tips of the Month.” The purpose of this new section of CHEST is to improve the ability of our potential authors to write in the most understandable and communicative manner possible and to enhance the understanding of our readers. As Dr. Richard Irwin noted in his recent editorials,3,4 the new focus and structure of CHEST includes a variety of new sections to educate our readers and to provide new areas of content.

To that end, we have recruited a group of highly experienced authors, editors, and biostatisticians to give us the benefit of their experience in a wide and, we believe, highly interesting range of topics concerning medical writing. Each month will bring you an article on a different topic. This should be of great interest and value not only to authors, but also to readers, enhancing the ability to critically appraise medical papers.

Articles in this section will essentially consist of two formats: one consisting of actual examples of poor communication (eg, “What is wrong with this . . . ?”), with suggestions for how they might be improved; and the other addressing concepts related to communications in the field of medicine, such as the “Uniform Requirements for the Submission of Manuscripts to Biomedical Journals” and publishing ethics. Please inform us of any topic that you particularly wish to be addressed, and we will try to include it on our scheduled menu.

This section is yet another aspect of the goal of CHEST to contribute to the area of education in the fields of pulmonary, critical care, and sleep medi-
Mixed vs Central Venous Oxygen Saturation May Be Not Numerically Equal, But Both Are Still Clinically Useful

Mixed venous oxygen saturation (SvO₂) in sepsis is commonly referred to as an end point of low impact on clinical decisions in sepsis patients because of the following common refrain: “SvO₂ is always increased in septic ICU patients.” However, there are fundamental principles that render this modality clinically useful when applying it to the supply-dependent phase of sepsis (ie, global tissue hypoxia). The presence of global tissue hypoxia not only has pathologic significance in vitro, but there is a pathologic link among the clinical presence of global tissue hypoxia (ie, low SvO₂ and cardiac index), the generation of inflammatory mediators, and mitochondrial impairment of oxygen utilization that is seen in septic ICU patients. Furthermore, identifying sudden episodes of supply dependency in septic ICU patients (ie, sudden decreases in SvO₂) has diagnostic and prognostic significance. With this background, the rationale for using central venous oxygen (ScvO₂) saturation as a surrogate for SvO₂ to detect and treat global tissue hypoxia in the most proximal phase of sepsis management (supply dependency) was the basis for its use in the Early Goal Directed Therapy in Severe Sepsis and Septic Shock Study (EGDT). Early hemodynamic assessment using physical examination, vital signs, central venous pressure, and urinary output fails to detect supply dependency or persistent global tissue hypoxia. Shock patients who are resuscitated to having normal vital signs continue to exhibit evidence of global tissue hypoxia (ScvO₂ < 70% and increased lactate levels) and require additional resuscitation, as shown by Rady et al. Similar findings were confirmed in the EGDT study as 39.8% of the control group vs 5% of the EGDT group continued to have global tissue hypoxia after 6 h of resuscitation despite the fact that all patients attained the same vital sign goals (ie, MAP, > 65 mm Hg; CVP, > 8 mm Hg; urine output, 0.5 mL/kg/h). These findings of global tissue hypoxia, or “cryptic shock,” in patients have prognostic significance as this state was associated with a 56.5% in-hospital mortality rate. The therapeutic significance was realized as the EGDT patients received early and more aggressive therapy with fluids, RBC transfusion, and inotropic agents.

The question of whether the ScvO₂ is a numeric equivalent to SvO₂ has been examined in a number of studies, which continues to fuel this debate. These studies, including the trial by Chawla et al, have consistently shown that ScvO₂ values are (on average) approximately 5% higher than SvO₂ values, which is likely secondary to the contributions of deoxygenated blood from the coronary sinus. Recognizing this minor, yet consistent, difference allows the clinician to make an accurate assessment of global tissue hypoxia. Furthermore, the clinical utility of an end point of resuscitation is determined by whether it changes clinical practice, morbidity, and mortality in a cohort of patients under the rigors of an appropriately designed clinical trial. In other words, has this end point been calibrated to have clinical utility in the setting in which it is to be used? This was done with ScvO₂ in the EGDT study, in which the range of ScvO₂ values was 48.6 to 49.2%, with lactate levels of 6.9 to 7.7 mmol/L indicating significant supply dependency. Using the finding from Chawla et al, the ScvO₂ values would be extrapolated to 43 to 45%. Thus, irrespective of whether the ScvO₂ value equals the SvO₂ value, the presence of a low ScvO₂ level in patients with early sepsis portends increased morbidity and mortality, and correcting this value according to a consensus-derived algorithm improves morbidity and mortality. It should be further noted that, in this well-designed study by Chawla et al, the majority of the...
51 patients were not supply-dependent as the mean 
\(\text{SvO}_2\) values ranged from 67.6 to 70.5, and the 
corresponding \(\text{ScvO}_2\) values ranged from 71.9 to 77.0 
with no mention of lactate levels.

Examining studies comparing the numeric equivalency of 
\(\text{SvO}_2\) vs \(\text{ScvO}_2\), while of important academic 
value, does not address clinical utility. The concept 
of the approximately 5% numeric difference 
between \(\text{SvO}_2\) and \(\text{ScvO}_2\) values is not novel, and the 
Surviving Sepsis Campaign has acknowledged this 
by recommending obtaining an \(\text{SvO}_2\) level of 65% 
and/or an \(\text{ScvO}_2\) level of 70% in the resuscitation 
portion of its management of patients with severe 
sepsis and septic shock bundle.

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