Change in the BODE Index Reflects Disease Modification in COPD: Lessons From Lung Volume Reduction Surgery

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Does Screening for COPD by Primary Care Physicians Have the Potential to Cause More Harm Than Good?

Congratulations to the investigators of the Spirometry in Asthma and COPD: a Comparative Evaluation (SPACE) program for carefully describing the excellent methods, but disappointing results, of their Italy-wide study to determine whether office spirometry performed by general practitioners (GPs) improves the diagnosis of asthma and COPD. Since 2003, similar projects have been generously funded in the United States. The SPACE program, which enrolled 570 GPs, with spirometry training provided by 57 pulmonary specialists, did not find a significant advantage of office spirometry in improving the diagnosis of asthma and COPD in the primary care setting. However, a type II error cannot be excluded, since the enrollment of participating patients reached only about half of the goal determined by a priori sample size calculations.

For several decades, I have personally been involved in promoting the idea that primary care providers (PCPs) should perform spirometry in their office. In 2000, the National Lung Health Education Program recommended office spirometry for COPD case-finding for adult smokers being seen by their PCP. Since then, tens of millions of dollars have been spent by industry for both COPD case-finding in PCP settings and for screening programs designed to test very large samples of the general populations of cities or entire countries for airway obstruction. During the same period of time, the definition of COPD has been considerably broadened by the criteria of the Global Initiative for Chronic Obstructive Lung Disease guidelines (FEV$_1$/FVC ratio, < 70% [regardless of age and FEV$_1$ percent predicted]), so that two to three times the number of people from a population sample of adults now fit the new definition when compared to traditional definitions.

So, why should I now argue with success? What possible harm could be done by the widespread application of spirometry to detect COPD in its early stages? Members of the National Lung Health Education Program recognized the weak evidence base > 5 years ago and called for well-designed studies to determine whether PCPs could achieve acceptably low misclassification rates for airway obstruction when using simple office spirometers, and whether knowledge of spirometry results substantially improves smoking cessation rates. A new report from the Agency for Healthcare Research and Quality (AHRQ) emphasizes that this essential evidence remains lacking and goes further to state that no inhaled medications have been demonstrated to improve COPD outcomes when prescribed to patients with an FEV$_1$ of $>50\%$ predicted (Global Initiative for Chronic Obstructive Lung Disease stages 0, 1, and 2); and that many patients have been prescribed inhaled medications for COPD, chronic bronchitis, or emphysema, yet have entirely normal spirometry findings. The financial implications of these recommendations and guidelines are enormous. Long-acting bronchodilators (and ultra-long-acting bronchodilators) and inhaled corticosteroids that have been prescribed for the treatment of COPD have worldwide annual markets in the tens of billions of dollars, and cost about $100 per month for each elderly patient without insurance coverage.

Older adults in whom COPD has developed due to smoking often have either a recognized or a subclinical comorbidity (eg, cardiovascular disease, glucose intolerance, osteoporosis, and ophthalmic disease) that makes serious side effects, such as malignant arrhythmias and osteoporotic fractures, more likely when receiving long-term therapy with these inhaled medications and, at best, temporarily reduces dyspnea on exertion in some patients with severe airway obstruction. Smokers and PCPs may also think that an inhaled medication is a substitute for smoking cessation. Thus, psychological, economic, and physical harm are all possible when an “abnormal” spirometry result usually leads to a prescription for an inhaled medication in an adult smoker (with or without chronic cough, phlegm, or wheeze). On a population-wide basis, the possible benefits of the increased likelihood of smoking cessation, temporary symptomatic relief, and slightly reduced risk of a COPD exacerbation may.

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not overcome the costs of testing and treating, and the drug side-effects.\textsuperscript{10} However, the risk/benefit ratio may be better for individually selected patients and those who also have asthma.

The results of the SPACE study\textsuperscript{1} (see page 844) suggest that problems with office spirometry will remain even if medications for COPD are developed that substantially improve the course of COPD in its early stages, or if future studies demonstrate that knowledge of abnormal spirometry results substantially prompts physicians to offer more effective smoking-cessation interventions, and prompts patients to successfully quit smoking. Even when offered free training by local pulmonary specialists, free spirometers, and free spirometry supplies, only a fraction of GPs are interested in testing, and, of those GPs who are interested, only a small fraction of adult smokers (or asthmatic patients) in their practice are tested, even during the first few months of enthusiasm. Most quit performing spirometry tests altogether. Furthermore, the long-term accuracy of the office spirometers was not evaluated; the misclassification rates were not determined; and the cost, benefits, adherence, and side effects of the resulting interventions were not measured in this study.

I now agree with the authors of the superb AHRQ report\textsuperscript{10} that, until more conclusive studies are performed, spirometry should currently be offered only to those smokers with dyspnea on exertion, and that therapy with inhaled medications should be reserved for those patients with a large bronchodilator response (suggesting asthma), relief of dyspnea, or severe airway obstruction (ie, $FEV_1 < 50\%$ predicted) with a recent exacerbation that suggests a high risk of hospitalization during the subsequent year. The AHRQ report\textsuperscript{10} quotes large epidemiologic surveys showing that a surprising fraction of patients with a diagnosis of COPD have normal spirometry findings (ie, normal $FEV_1/FVC$ ratio and a normal $FEV_1$). Spirometry may add more value when the lack of airway obstruction (after therapy with albuterol) is used to rule out COPD, than it does to confirm COPD in a smoker with respiratory symptoms. Substantial financial savings and a reduction in serious drug side effects would result for both the misclassified individual patients and entire countries if severe airway obstruction were routinely confirmed before the prescription of chronically inhaled medications for COPD.

Perhaps the focus should shift for a few years from trying to convince PCPs to perform spirometry in their office to providing high-quality (accredited) respiratory care services in each community,\textsuperscript{15} to which PCPs can refer their patients with dyspnea due to asthma or COPD. These services could include convenient smoking-cessation programs, asthma education, spirometry, allergen skin testing, exhaled nitric oxide measurements, pulmonary rehabilitation, long-term oxygen therapy, and chronic disease management, all following evidence-based clinical practice guidelines. The AHRQ report\textsuperscript{10} should also prompt the National Heart, Lung, and Blood Institute to place a high priority on the funding of a large multicenter study to determine whether spirometry enhances the best practice of smoking cessation in the primary care setting.

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Change in the BODE Index Reflects Disease Modification in COPD
Lessons From Lung Volume Reduction Surgery

Since the studies of Fletcher and colleagues,1 the natural history of COPD has been associated with the accelerated progressive decline of FEV₁. FEV₁ became the defining feature of the disease, and because it predicted mortality, health costs, and exacerbations,2–4 it constituted the logical target for disease-modifying interventions. Unfortunately, the diagnosis of COPD mandates that there be minimal FEV₁ response to bronchodilators, thus making changes in FEV₁ very difficult to achieve.

It is time to change the way in which we define disease modification in COPD. Indeed, COPD is associated with clinical manifestations not closely related to the FEV₁, such as worsened dyspnea, reduction in exercise capacity, pulmonary hypertension, peripheral muscle weakness, and malnutrition.5 Furthermore, all of these factors appear to be more important predictors of mortality than FEV₁.6–9 Therefore, defining disease modification solely on the improvement on the FEV₁ does not reflect the clinical manifestations of the disease and its ultimate prognosis.

Borrowing from the experience of other medical fields, disease modification in COPD can be defined as any of the changes in a patient with COPD that are caused by an intervention. The changes should be maintained over time. If we accept certain patient-centered outcomes as important, changes in any of them should be conceived as disease modifying. One such intervention, lung volume reduction surgery (LVRS), was popularized by Cooper et al.10 as a therapy for COPD patients with primarily upper-lobe emphysema. Although the National Emphysema Treatment Trial11 did not confer survival advantage to the surgical group as a whole, it resulted in differences in health status and exercise capacity in favor of LVRS and, at least in patients with upper-lobe emphysema and poor exercise capacity, a difference in survival after 3 years. It would be extremely useful if there were "surrogate" markers that could detect changes in a relatively short period of time, and that were accurate in predicting patient outcome. In this sense that marker could become a tool in monitoring disease modification. The multi-dimensional index BODE that includes the body mass index (B), percentage of predicted FEV₁ (O), dyspnea (D), and the 6-min walk distance (E) is such a tool,12 as it predicts mortality better than FEV₁. Furthermore, the variables that contribute to the index are amenable to change by interventions and thus make the BODE a potential tool to use in the evaluation of disease-modifying interventions.

In this issue of CHEST (see page 873), Imfeld and coworkers13 evaluated the power of short-term (3 months) changes in the BODE index in predicting survival in 186 patients undergoing LVRS. Using C statistics, the postoperative BODE index was a better predictor of survival than FEV₁, dyspnea score, or 6-min walk distance. These results are in line with those reported by Cote and Celli,14 who showed that the BODE index can improve after pulmonary rehabilitation and that the magnitude of the change was predictive of survival.

In the last few years, there have been important changes in the way we view COPD. Unfortunately, the regulatory agencies, the medical public at large, and many in our midst still cling to the old concept that it is only by changing FEV₁ that we modify the course of the disease. Imfeld and coworkers are to be praised for helping show that there are disease-modifying interventions and that tools such as the BODE index can be used as markers defining ultimate outcome.

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Tobacco Dependence Treatment

Time To Change the Paradigm

Fifty years ago, I asked my radiologist father why many of my grade school friends shunned another who had asthma. “Well, David,” he responded, “most people, and many physicians, believe that a psychiatric disorder or a personality flaw causes asthma, even though the scientific evidence does not support that.”

Last summer, while presenting “Medical Management of Tobacco Dependence” at the house-staff noon conference at Stanford Medical, I related this story. Their eyes popped. Jaws dropped. They were astounded that 50 years ago anyone could have thought asthma was a psychiatric disease. After they recovered from their shock, I said I hoped that 20 years hence no one would believe the use of cigarettes was a manifestation of a flaw in character or a weak will. Rather, everybody—physicians and non-physicians—would approach tobacco dependence for the chronic medical disease it is, and recognizing cigarette use as the primary symptom of tobacco dependence.

In this article of CHEST (see page 979), Bars et al1 start the transformation in a phase II, open-label, proof-of-concept study testing the hypothesis that the number of cigarettes smoked per day determines the severity of tobacco dependence and consequently provides a way to provide more effective, individualized pharmacotherapy, rather than the standard “one-dose-fits-all” approach. Individualizing medication types, doses, and delivery systems, as well medication duration of use, is common in medical practice; clinical therapeutics for tobacco dependence, however, is mired in outmoded pharmacotherapeutic concepts. The clinical trial by Bars et al1 on tobacco dependence is one of the first to break out of that mold, using a treatment paradigm similar to asthma: individualizing treatment based on disease severity.

For having the scientific guts to break with entrenched (and nonscientifically validated) tradition within the field of tobacco dependence, these authors are to be commended. Their findings are of critical importance to developing a more practical and more clinically effective treatment model for improving medical treatment of tobacco dependence.

Despite the documented safety and effectiveness of any pair-wise combination of US Food and Drug Administration-approved tobacco dependence medications, boosting treatment effectiveness an additional 50 to 100% over either medication alone,2–9 physicians do not routinely use medication combinations to improve outcome results. The most likely reason for this omission is the lack an algorithm to determine what medication combinations to use and when, hence the importance of the present study.

The authors1 chose number of cigarettes smoked per day as the independent variable to determine the initial medication doses and delivery systems. Thus, the “average” tobacco-dependent patient, comprising 50% of this group from the New York Fire Department (FDNY), smoked 20 to 30 cigarettes per day and would have started treatment on two different nicotine medications: an oral inhaler at \( \leq 12 \) cartridges per day, and a patch delivering 15 mg of nicotine over 16 h. Since each inhaler cartridge can deliver up to 4 mg of nicotine, the total daily nicotine dose for the typical FDNY firefighter could have been 63 mg of nicotine per day, a threefold- to fourfold-higher dose than nicotine patch labeling would recommend. Informatively,
slightly > 10% of the firefighters smoking 20 to 30 cigarettes per day actually used a more intense regimen, since only 44%, not 50%, used the initial regimen.

The nicotine patch functions like an asthma controller medication and generally cannot relieve acute, breakthrough, nicotine-withdrawal symptoms. Nicotine patch takes a long time to reach maximum serum concentration (TMAX) [both arterial and venous] of 6 to 8 h.10 The nicotine inhaler is 16 times faster: TMAX = 30 min.11,12 This oral inhaler delivers nicotine to the brain faster and can thus relatively acutely relieve breakthrough nicotine-withdrawal symptoms. The nicotine oral inhaler does function precisely like an asthma rescue inhaler.

In contrast, the light-smoking NYFD members, smoking only one to five cigarettes per day, comprised 5% of the study population. They would have started on only the nicotine inhaler, up to six cartridges per day, delivering only ≤ 24 mg of nicotine per day: a 62% less total daily nicotine dose than the typical tobacco-dependent patient in this cohort would receive. This approach is similar to using an albuterol inhaler as an as-needed rescue medication to treat mild, intermittent asthma.

The heavy-smoking FDNY firefighter, smoking > 40 cigarettes per day and comprising only 5% of the study population, would have started on one controller medication (a higher patch dose [two patches], delivering 30 mg of nicotine over 16 h) and also two different nicotine-withdrawal symptom rescue medications: the oral inhaler (≤ 12 cartridges per day) and the nicotine nasal spray for immediate/crisis withdrawal symptom relief. Most importantly, as the authors1 point out, four times more firefighters than predicted—even though smoking < 40 cigarettes per day—needed this unique, high-dose nicotine medication paradigm in order to keep nicotine-withdrawal symptoms adequately suppressed. This group would have used a total nicotine medication dose of 78 to 100 mg of nicotine per day, four to seven times more than the ubiquitous, nonscientifically determined nicotine patch labeling states: 15 mg over 16 h or 21 mg over 24 h. Because nicotine medication doses were individualized, side effects were nil.1

Finally, the protocol allowed for the addition of a second controller medication, sustained-release bupropion, 150 mg, bid. As Table 1 in the article by Bars et al13 stated, 14% of enrollees used sustained-release bupropion, with most smoking > 40 cigarettes per day. Thus, it would appear that 14% of the firefighters needed two controller medications, including 30 mg of nicotine over 16 h transdermally, and up to 88 mg of additional nicotine via rescue medication delivery systems to keep nicotine-withdrawal symptoms under adequate control.

Bupropion has a unique CNS mechanism of action. It is both a dopamine and norepinephrine reuptake inhibitor but without effect on serotonin.13 Nicotine, in contrast, activates multiple CNS pathways to release dopamine and norepinephrine, as well as other neurotransmitters.14 These two tobacco dependence-controller medications, sustained-release bupropion and nicotine patch, each acting via different pharmacologic mechanisms of action in the CNS, are similar to using two controller medications in asthma.

Use of an algorithm of this type confirms two important points: (1) individualizing and tailoring medication combinations and doses, similar to the current asthma standard-of-care, improves tobacco dependence treatment effectiveness. Essentially every published study heretofore found that treatment effectiveness was inversely proportional to the number of cigarettes smoked per day. The worst smoking cessation rates were seen in those who, pretreatment, had smoked > 20 cigarettes per day. Moreover, the number of cigarettes smoked per day, pretreatment, inversely predicted the percentage not smoking at any time after treatment start. Dale et al15 found this relationship highly significant (p < 0.0001) across all doses of sustained-release bupropion studied. Table 115 shows that 33% of patients randomized to placebo who had smoked ≤ 19 cigarettes per day had stopped smoking at the end of study drug treatment, while only 4% who had smoked ≥ 40 cigarettes per day could stop. Figure 4 in the study by Bars et al1 demonstrates that the novel approach eliminates that inverse relationship. At 3 months, approximately 50% of those who had smoked 6 to 19 cigarettes per day had stopped, as had approximately 50% who had smoked > 40 cigarettes per day. Even more remarkable, at the 12-month evaluation point,1 9 months after all treatment had stopped, treatment effectiveness was directly proportional to the pretreatment number of cigarettes per day: approximately 30% of those who had smoked 6 to 19 cigarettes per day had stopped, but nearly twice that (approximately 50%) who had smoked > 40 cigarettes per day had stopped. This finding is truly remarkable and without precedent. If subsequent, randomized, double-blind studies confirm the unique, individualized approach of Bars et al,1 we will be able to safely provide far more effective tobacco dependence treatment for the patients in our office.

(2) Individualizing the dose of nicotine to as high as ≥ 100 mg/d is safe, with no study participant having a serious adverse drug event. The adverse events reported were of mild intensity and little
consequence.1 If anything, these adverse events seemed to relate more to resuming cigarette smoking, rather than use of nicotine medications.1 The adverse events of greatest potential cardiac concern, chest pain and palpitations, fell significantly over time, and particularly—surprise!—among those who stopped smoking.1 It appears that even use of up to 100 mg of nicotine per day in the heaviest of smokers did not produce toxicity.1

This study provides strong, compelling evidence that individualizing pharmacotherapy can substantially improve tobacco dependence treatment effectiveness, with the heaviest cigarette users enjoying 50% treatment effectiveness—results unheard of before the present study. The authors1 rightly point out that their approach, based on number of cigarettes smoked per day at study entry, although intuitive and easy to employ, was not optimal. Rather, the intensity of nicotine withdrawal, as easily measured by the Fagerström Test for Nicotine Dependence,16 and the intensity of nicotine-withdrawal symptoms, after stopping smoking, should provide a superior algorithm to optimize treatment results.

This study shows us it is time to shed the artificial and scientifically invalid dose and duration-of-use constraints posed by nicotine medication labeling and focus our attention—30 years after nicotine polacrilex gum arrived on the global market—where it should be: combining these valuable and safe medications, including nicotine and bupropion, in the most effective ways and using them as long as necessary17–19 to improve smoking cessation rates and optimize tobacco dependence treatment outcome. After all, providing effective treatment so that our patients have the proper tools to stop smoking is the only way to prevent the progression of COPD.20,21

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When Pulmonary Embolism Treatment Isn’t Working

Objectively proven acute pulmonary embolism (PE) is a satisfying disease to treat—unless the treatment isn’t working. Supplementary oxygen for the ventilation-perfusion component of hypoxia, urgent anticoagulation IV or subcutaneously, and intensive care for patients with more profound abnormalities are relatively easily accomplished. Intensive care may include IV, peripherally administered thrombolysis (absent a serious or absolute contraindication) and IV crystalloid and pressor, with careful attention to right ventricular filling, titrated to support cardiac output.

But some patients, including some without prior known cardiopulmonary impairment, don’t improve. Some worsen. When the evidence-based treatment armory appears to be failing, deep concern ensues. While we’re aware that about 12% of PE patients will die from it,¹ that outcome is difficult to accept from a nonmalignant disease so frequently and carefully studied and usually handled so well. Of other treatments to try at this stage, there is only one the average intensivist can employ without calling another specialist to urgently assume control of the patient—repeat thrombolysis.

Repeat thrombolysis is not commonly employed worldwide and there is no consensus about its use. One recent metaanalysis of thrombolysis in PE did not report any repeat thrombolysis,² nor is it mentioned in either of two reports of large PE registries³,⁴. A randomized, partially blinded multi-center trial of PE treatment from German centers⁵ found it used 8% of the time in deteriorating patients but our impression is that it is uncommonly used in North America. North American physicians are more likely to try other techniques, such as percutaneous embolectomy, catheter fragmentation, angioplasty, and thrombectomy,⁶ whose rationale is rapid relief of central pulmonary artery obstruction by dispersion of central clots to the periphery. Percutaneous catheter embolectomy has also been reported to have a higher success rate and lower mortality than surgical embolectomy; surgery has a previously reported average mortality of 30%,⁷ although sporadic and more recent reports show improvement over that figure.⁷,⁸

Concurrent controls are more valid than historical ones. Desperate as we are to save the otherwise salvageable patients dying from PE despite our evidence-based treatment, who among us is using acceptable methodology to study how to do that?

Meneveau and colleagues⁹ have done so and carefully documented a concurrently-controlled series in this issue of CHEST (see page 1043). Although their comparison of surgical thrombectomy on cardiopulmonary bypass vs repeat systemic thrombolysis is neither randomized nor blinded, this one-of-a-kind report of a substantial number of patients failing first thrombolysis provides important clinical guidance. Meneveau et al’s hospital dealt with failed thrombolysis in one of two ways: repeat thrombolysis or open surgical removal of clot with a forceps while the heart was beating. The populations undergoing one treatment or the other were similar, though not identical—for example, there was a higher proportion of patients with shock in the surgical group. Results of other interventions such as mechanical catheter fragmentation, percutaneous suction embolectomy, secondary thrombolytic infusion directly into a central clot, and of other possible techniques are not reported in the paper. That should not be viewed as a weakness of this report—too many centers have no planned fallback management plans whatsoever for such patients. There are other aspects that make the study’s results inconclusive besides heterogeneity of the patient populations: lack of a statistically significant survival benefit, wide confidence intervals around major bleeding rates and outcome, and the multitude of uncertainties that attend results of nonrandomized interventions. But there is an observable trend toward a better in-hospital outcome with rescue surgical thrombectomy.

The surgical management of such patients may not be straightforward either. The objective is to establish hemodynamic stability with sufficient flexibility to deal with the particular circumstances found in the individual patient. Unless impossible, re-imaging after failed thrombolysis should be done to establish that surgically accessible clot remains proximal to the first pulmonary artery branches. median sternotomy provides the best exposure and cardiopulmonary bypass the best likelihood of stabilizing the circulation. Ascending aortic and dual caval cannulations to minimize blood in the operative field (or faster right atrial cannulation if there is less time) give the surgeon best control—this is precisely the technique reported by Meneveau et al (others have reported femoral-femoral bypass instituted percutaneously for early stabilization¹⁰). Although cooling the heart and cardiac arrest might provide better myocardial protection, they take extra time which may confer significant additional risk, and these surgeons didn’t employ them. Clot removal by ring forceps, and, on occasion, cautious gentle balloon extraction of more
distal clot (balloon extraction not reported by these authors) can be employed. More distal clot can be removed with circulatory arrest and under direct vision but the bleeding risk is increased (Meneveau et al did not do this). Skin-to-skin time, if things go well, is about 1 h.

Some surgeons might consider embolectomy off-pump11 but must be comfortable with that approach. There is little if anything written about embolectomy after systemic thrombolysis—bleeding has been greatly feared, although there are case reports of safe application of lytics after surgical embolectomy.12,13 As a practical matter, with the lytics off by the time the patient reaches the surgical suite, their impact could be minimal. These authors reported operating within 72 h of lytic administration and had no fatal bleeds in the 14 rescue embolectomy patients, indicating that prior lytics is not an absolute contraindication.

This carefully documented report shows the modern feasibility of rescue surgical embolectomy after failed thrombolysis for PE. It includes a comparison to the alternative previously reported strategy of repeat thrombolysis. Importantly, it provides a foundation for physicians caring for PE patients at centers with cardiothoracic surgery to meet and formulate plans for how and when to call for help and what kind of help to call for. These patients often present in extremis after iatrogenic interventions intended to help them (eg, bariatric, joint replacement, or cancer surgery, or chemotherapy). Determining local criteria and detailed plans for rescuing PE patients who fail usual treatment is an important priority for our specialties. Further cooperative clinical studies should ensue. We congratulate Meneveau and colleagues for a carefully documented report of great practical use.

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Second-Line Chemotherapy for Non-small Cell Lung Cancer

The article by Chen et al1 (see page 1031) is highly instructive from a number of perspectives. First and foremost, the authors (and the reviewers) failed to emphasize that this is a randomized phase II trial and not a randomized phase III trial. Phase III trials are true comparison trials and are sized so that clear inferences can be made about the superiority (or lack thereof) of any of the study arms tested. Randomized phase II trials are designed to choose the best option from among several with similar expected outcomes and to test the feasibility of randomizing across different modalities. They are, in reality, parallel phase II trials. The required numbers for these trials are far smaller than phase III trials. Their major use is in eliminating the problems inherent in interpreting the outcome of multiple phase II trials done at separate institutions. It is not statistically valid to

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draw conclusions based on comparisons between the study arms. Consequently, the inter-arm comparisons in this trial are invalid, although an actual phase III trial confirmed these findings.4 Despite that, there are several useful lessons from this trial.

The major lesson for pulmonologists from this article is that second-line (and even third- and fourth-line) therapy for metastatic non-small cell lung cancer is common and reasonable for patients who remain in “good” condition and who desire further treatment.5-7 This is an important change in clinical perspective. A decade ago, there were essentially no active regimens for patients who failed first-line chemotherapy. Indeed, up to the mid 1990s, the response rate for first-line chemotherapy was only on the order of 20 to 25%, and only 25% of patients with metastatic disease survived > 1 year.8 Following the introduction of the taxanes, gemcitabine and navelbine, in the mid-1990s, the response rates have climbed and 1-year survival is closer to 50%, with 20 to 30% of patients with metastatic disease surviving ≥ 2 years.9,10 The later introduction of the epidermal growth factor receptor (EGFR)-targeted agents, gefitinib and erlotinib,11 has added another level of response and disease control that has served to prolong survival in the second-line setting. Most recently the addition of bevacizumab, an angiogenesis inhibitor, to paclitaxel plus carboplatin resulted in a significant improvement in survival, although there is a small subset of patients with severe and even fatal hemorrhage.12 When I first joined the American College of Chest Physicians in 1993, there were still debates about whether patients should receive any chemotherapy for metastatic lung cancer. We are, thankfully, well beyond those discussions as demonstrated by the appearance of this article in CHEST (see page 1031).

Docetaxel was, for a period, the only agent approved by the US Food and Drug Administration (FDA) for this indication, and that is a lesson in itself. The FDA approval process bears no relationship to the actual utility of any regimen compared to another. The company need only show that the outcome is superior to no treatment or to some other inferior therapy. Several other agents are now approved for use in this setting, including pemetrexed (an antifol13) and erlotinib (an EGFR inhibitor11). Pemetrexed has been shown to have equal efficacy with lower toxicity in a phase III randomized trial.14 In practice, oncologists try to choose a regimen that is non-cross-resistant with the regimen that just failed and which the patient can tolerate. The data on weekly therapy have been a bit confusing. There are no reports that it is superior to traditional every 3-week therapy, only that in some settings that it may be less toxic.

A second lesson from this trial is the importance of pharmacogenomics. It is clear that Asian patients have very different response rates and toxicities to several common chemotherapy regimens including docetaxel14 and other taxanes.15 In addition, the response rate to the EGFR inhibitors, gefitinib or erlotinib, is significantly higher in Asian patients, especially young, female patients who have lung cancer despite a negative smoking history.16 This has now been correlated with a much higher rate of EGFR mutations in this group of patients.16 This is not an issue of racial profiling; it is a matter of what works and doesn’t work in patients, and needs to be factored in to studies and day-to-day clinical decision making.

It is frustrating that this article was not the randomized study that we need but rather another tidbit of information that suggests benefit. Despite at least one true randomized trial5 suggesting equal efficacy and lower toxicity, the type II error is large enough that significant differences may still exist that favor more intensive doses every 3 weeks. It is not yet time to leap to the conclusion that weekly therapy is better. The only certainty we have to date is that the reimbursement for weekly therapy is superior.

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Understanding Vocal Cord Dysfunction

A Step in the Right Direction With a Long Road Ahead

In this issue of CHEST (see page 905), Mikita and Parker demonstrate that ambulatory vocal cord dysfunction (VCD) patients, who likely had an underlying somatoform disorder, had significantly more physician visits and subspecialty visits (particularly pulmonary) during the year prior to their VCD diagnosis than matched control subjects with moderate persistent asthma, which is the disorder that VCD often mimics.

The VCD diagnostic approach of Mikita and Parker is impressive from two perspectives. Because of their role in determining soldier fitness for duty, they implemented an aggressive evaluation for unexplained dyspnea, typically including a comprehensive assessment for bronchial hyperreactivity. Consequently, they were able to exclude concomitant asthma in 84% of their 25 VCD patients. Ironically, the identified VCD patients were largely retirees and dependents rather than active duty military.

Second, the authors state that they followed the standardized laryngoscopic procedure and diagnostic criteria for VCD. These criteria evolved from the endoscopic findings that we described in 1983 in the first report of VCD presenting as asthma. To summarize, when laryngoscopy is performed utilizing adequate topical anesthesia in symptomatic patients, the presence of inspiratory or expiratory vocal cord adduction with a posterior glottic chink confirms the diagnosis of VCD. The findings are illustrated in Figure 1.

It is of concern that the present study reveals that VCD was not recognized despite multiple encounters with pulmonary physicians over the year prior to diagnosis. So why is it that, after all these years, there is such difficulty in understanding and diagnosing VCD?

The first answers are obvious: (1) it is a relatively uncommon condition; (2) the disorder closely mimics asthma; (3) intermittent symptoms make endoscopic confirmation logistically difficult; and (4) by the very nature of a somatoform disorder, diagnosis of the condition is elusive. Another problem is that the definition of the term VCD has also become elusive. We originally selected the term VCD to identify a very specific clinical syndrome that had defined endoscopic features and mimicked asthma. Over time, VCD has become a very loosely applied descriptor for inspiratory or isolated expiratory vocal cords.

Figure 1. Laryngoscopic findings obtained during inspiration in a symptomatic patient shows adduction of the true vocal cords anteriorly, and the glottis narrows to a small posterior diamond-shaped chink. An additional feature is that the false vocal cords adduct, obscuring the laryngeal ventricles.
cord adduction, either with or without the presence of the posterior chink. Furthermore, the term VCD has been applied to an ever-expanding array of clinical presentations. There are a number of additional diseases or disorders that are manifested by abnormal vocal cord motion during breathing. They likely have different medical or psychological etiologies and constitute a spectrum of clinical presentations with varying severity. Confusion will continue if a spectrum of disorders is collectively lumped together as VCD.

Clarity is further obscured if what has been loosely identified as VCD limited to the expiratory phase may not be dysfunctional at all. Adduction of the vocal cords at the end of exhalation is normal.² Higenbottam⁴ demonstrated that adduction of the vocal cords occurred in early exhalation when healthy volunteers underwent histamine bronchoprovocation. Though expiratory vocal cord adduction in patients with obstructive lung disease may be pathophysiologic under certain conditions, we should not jump to conclusions. Higenbottam⁵ showed that patients with airway obstruction had early expiratory adduction of the vocal cords. The most marked expiratory adduction occurred with the lowest FEV₁ values. Collett and coworkers⁶ showed that vocal cord adduction occurs during mid-exhalation in asthmatic patients with experimentally induced bronchoconstriction. The key insight is that the reversal of the glottic obstruction occurred with continuous positive airway pressure. This finding suggests that expiratory adduction in asthma patients may contribute to hyperinflation, allowing a beneficial reduction in persistent inspiratory muscle activity during exhalation.

Confusion persists regarding the potential coexistence of asthma in patients with a somatoform disorder that meets the laryngoscopic criteria for VCD. In these patients, glottic obstruction often occurs on expiration as well as on inspiration. Therefore, expiratory flow may be limited on spirometry and may mimic asthma. Figure 1 in the original description of this disorder³ shows obstruction of the expiratory flow-volume relationship in addition to inspiratory flow limitation in patient 5. The study was performed while the patient was symptomatic, and the results could be interpreted as VCD with concomitant asthma. However, subsequent bronchoprovocation studies excluded asthma. The pitfalls of diagnosing concomitant asthma based on an expiratory obstructive pattern on spirometry and bronchoprovocation studies have been recognized.²,⁷–⁹ Noninvasive, practical, reliable, appropriately sensitive, specific, and easily interpreted tools that allow partitioning of the resistances in the upper and lower airways are needed to further our understanding of the physiologic and pathophysiologic roles of the larynx in lung disease.

The message is clear. We need to move away from using the term VCD as a catch-all descriptor for vocal cord adduction during breathing. A greater understanding of physiologic vs pathophysiologic alternations in the glottic aperture is required. Future prospective studies must objectively, meticulously, and precisely define other diseases and disorders affecting the glottis during breathing. We need to become “splitters” rather than “lumpers.” Physiologic and anatomic correlations are key.

Though the prevalence of VCD is low, Mikita and Parker¹ have confirmed a significant negative impact on health-care utilization. The plethora of case reports are testimony to impaired quality of life. It is high time to conduct appropriate scientific inquiries, including prospective, comprehensive multicenter trials at institutions with the commitment and resources that are necessary to maximize our understanding of conditions that have been collectively lumped together under the term VCD.

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