Chronic Obstructive Pulmonary Disease: Emerging Medical Therapies

Neil R MacIntyre MD

As many as 10 million Americans have chronic obstructive pulmonary disease and as a consequence experience disabling symptoms, high cost of care, and substantial mortality. Several new approaches are being investigated for possible benefit in managing (or even reversing) chronic obstructive pulmonary disease. This article reviews 4 new approaches that are either in or close to phase III trials: long-acting bronchodilators, phosphodiesterase-4 inhibitors, vasodilators, and retinoids. Of those tiotropium appears to be the closest to receiving clinical approval in the United States. The risk/benefit ratio and the cost-effectiveness of the other compounds are less clear and await additional study. *Key words: chronic obstructive pulmonary disease, COPD, bronchodilator, phosphodiesterase inhibitor, vasodilator, retinoid, retinoic acid.* [Respir Care 2004;49(1):64–69.

Introduction

Chronic obstructive pulmonary disease (COPD) continues to be a major cause of morbidity and mortality in millions of patients around the world.[1] Although clearly the best way to manage this disease process is to prevent it (through avoidance of tobacco smoke), the health care system has become heavily burdened by the care required for those who have been unable to do that. At the present time, there are a number of strategies to manage the disabling symptoms of COPD. Pharmacologic therapy for COPD has been reviewed extensively in evidence-based guidelines such as the American Thoracic Society statement[2] and the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] and are discussed in more detail in Dr Heffner's report to this Journal Conference.[4] Pulmonary rehabilitation programs emphasizing education, exercise, and psychosocial support also significantly improve functional capacity and quality of life in COPD patients.[5] More recently, 2 surgical procedures have been found to significantly benefit selected COPD patients: lung-volume-reduction surgery for selected patients with heterogeneous emphysema[6] and lung transplantation for end-stage COPD.[7]

In this report I will review emerging medical therapies for COPD. Specifically, I will review new pharmacologic agents that have shown enough promise that they are either in or near phase III trials. In contrast, I will not be reviewing off-label applications of approved drugs used in other respiratory and nonrespiratory diseases (eg, leukotriene modifiers, isomers of albuterol, surfactants, and anti-inflammatories). Though those approaches may have utility in COPD, the supporting data are limited.

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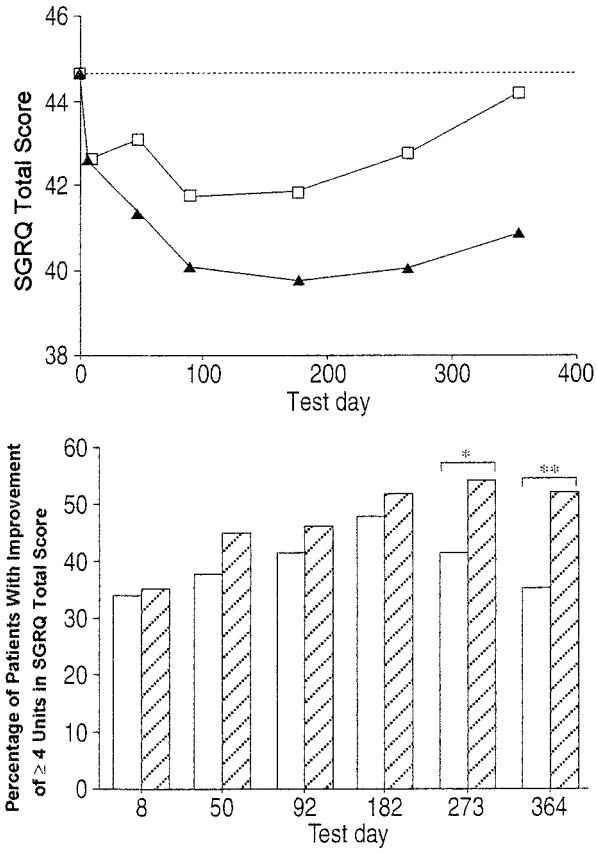

Fig. 1. Top Panel: Health-related quality of life, as reflected in the St George' Respiratory Questionnaire (SGRQ) score (a lower score is better) in patients during a 1-year trial comparing tiotropium (triangles) to ipratropium (squares). Bottom Panel: Percentage of patients in the ipratropium group (clear bars) and the tiotropium group (hatched bars) who had SGRQ total score improvement of ≥ 4 units. (From Reference 10, with permission.)

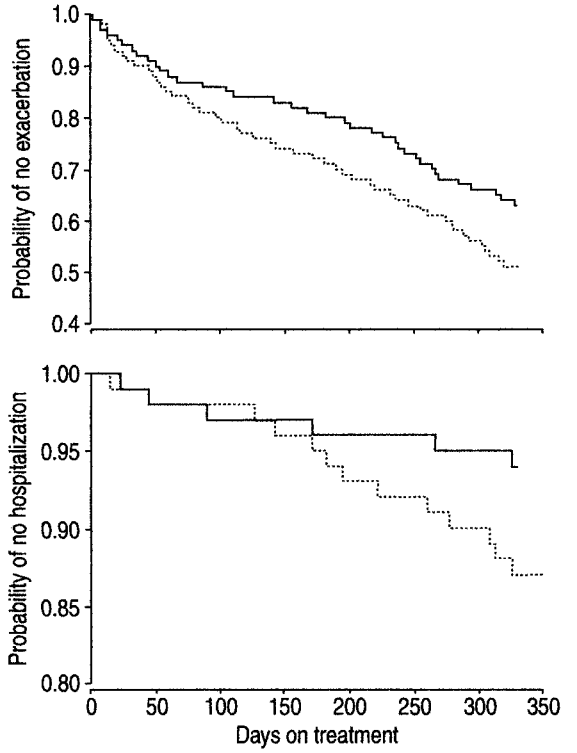

Fig. 2. Probability of exacerbations (top panel) and hospitalizations (bottom panel) in patients during a 1-year trial comparing tiotropium (solid lines) to ipratropium (dashed lines). (From Reference 10, with permission.)

Extended-Action Bronchodilators

There are 2 long-acting bronchodilators with promise for COPD: tiotropium and the R,R isomer of formoterol. Of these, tiotropium is closest to clinical approval; indeed, it is already on the market in Europe.

Tiotropium is an anticholinergic compound that is delivered via aerosol and has low systemic absorption.[8] By reducing cholinergic tone, airway mucus secretion and bronchial muscle tone are reduced.[8,9] Tiotropium has a slower dissociation from muscarinic receptors than does the currently-available drug, ipratropium, and this allows once-per-day administration.[8,9] Tiotropium's only adverse effect appears to be dry mouth.

Two large clinical trials have demonstrated the benefits of tiotropium. The first, by Vincken et al, compared daily tiotropium to 3-times-daily ipratropium.[10] That study found that both drugs have good acute effects on forced expiratory volume in the first second (FEV_1) and that no tachyphylaxis develops over a year of use. The study also showed that the tiotropium effect lasts a full 24 hours, unlike ipratropium. Tiotropium was also superior to ipratropium with regard to quality-of-life scores and health care utilization (number of exacerbations and hospitalizations) (Figs. 1 and 2).

The second large trial, by Casaburi et al, compared tiotropium to placebo[11] and found that daily tiotropium improved dyspnea score, quality of life, and FEV_1.

Importantly, both of those trials showing benefit from tiotropium used the tiotropium in conjunction with β agonists and other standard COPD therapies. This suggests that tiotropium will be an addition to current therapies rather than a replacement (except perhaps for ipratropium). Supporting this concept is a recent abstract suggesting that the combination of tiotropium with a long-acting β agonist is superior to either drug alone.[12]

(R,R)-formoterol is the L isomer of formoterol, a long-acting β agonist.[13] It can be delivered as an aerosol without (S,S)-formoterol, the isomer associated with toxicity and bronchoconstriction. Thus, there is the potential for once-per-day administration and better patient tolerance. Because this drug is still in phase III clinical trials, it is impossible at present to comment about what its role will be. Nevertheless, a once-per-day β agonist would certainly

be an important addition to our armamentarium against COPD.

Phosphodiesterase Inhibitors

Airway inflammation in COPD involves neutrophils, macrophages, and cluster-of-differentiation-8 (CD8)-positive T cells. Cyclic adenosine monophosphate (AMP) within these cells attenuates many of these inflammatory processes (as well as airway smooth-muscle tone). The family of enzymes known as phosphodiesterases (PDE) break down cyclic AMP. PDE inhibitors block this breakdown and thereby reduce inflammation and smooth-muscle tone.[14,15] There are at least 12 known groups of PDE inhibitors, with PDE group 4 most specific for airway cells.

A number of PDE4 inhibitors have been studied, and two (cilomilast and roflumilast) have phase III trial data available.[16–18] Of the two, roflumilast has the higher PDE4 binding affinity and more universal PDE4 inhibition among the various cells involved in airway inflammation.[19]

Cilomilast, however, has been in clinical trials longer.[20,21] The largest published randomized, controlled trial was reported in 2001; it involved 424 patients for 6 weeks.[20] Cilomilast at 15 mg twice a day showed small but significant FEV_1 improvement (0.10–0.15 L) over placebo, as well as a trend (not reaching statistical significance) towards better quality-of-life score with cilomilast.

The clinical trials of roflumilast are more recent and still only in abstract form.[22,23] The results, however, appear to show that once-daily roflumilast improves FEV_1 significantly more than placebo,[22] reduces COPD exacerbations in a dose-dependent fashion,[22] and the incidence of adverse events is not higher than placebo.[23]

Taken together, those clinical trials suggest that PDE4 inhibitors do have a real FEV_1 effect, largely by reducing inflammation, but whether these relatively small physiologic responses translate into truly improved outcomes is still open to question. Moreover, although preliminary adverse effect profiles of the newer PDE4 inhibitors appear good, older prototype PDE4 inhibitors had substantial adverse effects, with the most notable being headache and nausea. Trials comparing PDE4 inhibitors to current strategies (not just placebo) using meaningful clinical outcomes (not just FEV_1) will be needed to determine if these drugs are an important addition or replacement medication in COPD treatment.

Vasodilators

There are a number of vasodilators available that have selectivity for the pulmonary vascular system. Among these are nitric oxide (NO), NO donors and analogs, prostacyclin and prostacyclin analogs, endothelin modulators, and angiotensin antagonists. A number of these have shown benefit in various diseases of the pulmonary circulation, such as pulmonary hypertension.

Table 1. Inhaled Nitric Oxide in the Treatment of Chronic Obstructive Pulmonary Disease

Variable	Oxygen Only (n = 17)		Oxygen Plus Nitric Oxide (n = 15)	
	Before	After	Before	After
Mean PAP (mm Hg)	25	25	28*	21*
Cardiac output (L/min)	5.5	5.3	5.6	6.1
PVR (dyn·s·cm^{-5})	259	264	273*	177*
PCWP (mm Hg)	10	9	10	8
Mean BP (mm Hg)	92	91	94	95
P_{O_2} (mm Hg)	80	74	73	71
FEV_1 (L)	1.29	1.28	1.09	1.07
% "improved"	NA	12.5†	NA	38.5†

PAP = pulmonary artery pressure
PVR = pulmonary vascular resistance
PCWP = pulmonary capillary wedge pressure
BP = systemic blood pressure
FEV_1 = forced expiratory volume in the first second
*$p < 0.05$ for before and after values.
†$p < 0.05$ between the 2 groups.
(Data from Reference 27.)

Inhaled NO has been studied the most with COPD.[24] In addition to NO's vasodilating properties, it may also regulate mucus production and even bronchodilate. In theory the vasodilation may help ventilation/perfusion matching and thus improve gas exchange in COPD patients. Moreover, the vasodilating properties would help reduce pulmonary vascular resistance and help unload the right heart in patients with secondary pulmonary hypertension and cor pulmonale. These vasodilating effects, however, can cause pulmonary and airway edema. Moreover, NO can be pro-inflammatory, through various mechanisms, including the formation of toxic radicals. Interestingly, steroids, thioles, and xanthine oxidase inhibitors may help modulate this balance between benefit and harm.

Inhaled NO can be delivered in pulses of up to 100 ppm via nasal cannula. Under these conditions NO is an effective vasodilator, with effects comparable to oxygen and intravenous prostacyclin.[25] In short trials with patients with elevated pulmonary vascular resistance from COPD, inhaled NO reduced pulmonary vascular resistance.[26]

The largest clinical study of inhaled NO in COPD patients to date was a randomized, controlled trial of 40 patients with secondary pulmonary hypertension.[27] All the patients were on oxygen and were randomized to receive, for 3 months, either oxygen alone or pulsed NO (at 20 ppm) along with their supplemental oxygen. Right heart catheterization was done in all the patients. Table 1 summarizes the data. There was a significant reduction in mean

pulmonary artery pressure and pulmonary vascular resistance with inhaled NO. Although not assessed in a formal fashion, there also appeared to be an increase in the number of patients who felt they were "improved" while using inhaled NO.

Larger trials with meaningful clinical outcomes will have to be done before the role of NO in COPD is firmly established. Indeed, because of the potential toxicities of NO, better vasodilators may need to be developed and tested in order to treat this particular aspect of COPD.

Promoting Alveolar Repair

A characteristic of emphysema is alveolar destruction. Agents that can re-induce morphogenesis may have considerable potential in literally rebuilding the alveoli in COPD. One set of compounds that appears to have this potential are the retinoids.[28–30] These substances function like hormones to regulate cell proliferation, cell differentiation, and morphogenesis. They are key molecules in wound repair, where they stimulate fibroblast proliferation and matrix deposition. They also play a role in apoptosis in this process. Indeed, retinoids have found a number of dermatologic applications, for promoting wound healing and reversing/preventing aging effects and epidermal atrophy.

It is conceivable that retinoids may do similar things in the lungs. A number of in vitro studies have demonstrated that growth of alveolar tissue can be stimulated by retinoids (although the effects are more pronounced on the interstitial matrix than on the elastic structures).[31,32] Retinoids may also block elastase effects, which may be important in the development of emphysema.[33]

Perhaps the most well known animal studies are those by Massaro and Massaro,[28,31,32] in which elastase was instilled into the lungs of rats to produce emphysema. If retinoic acid was given to these rats, even many days after the induction of the elastase injury, substantial regeneration of alveolar structures took place (Fig. 3). Because rats, unlike humans, have the ability to naturally grow alveoli throughout their life spans, it is not clear whether these effects will translate into benefit for COPD patients. Moreover, retinoids can have substantial adverse effects, including skin lesions, headache, transaminitis (although there are no reports of permanent liver damage), hyperlipidemic states, teratogenicity, and carcinogenesis (including lung cancers).

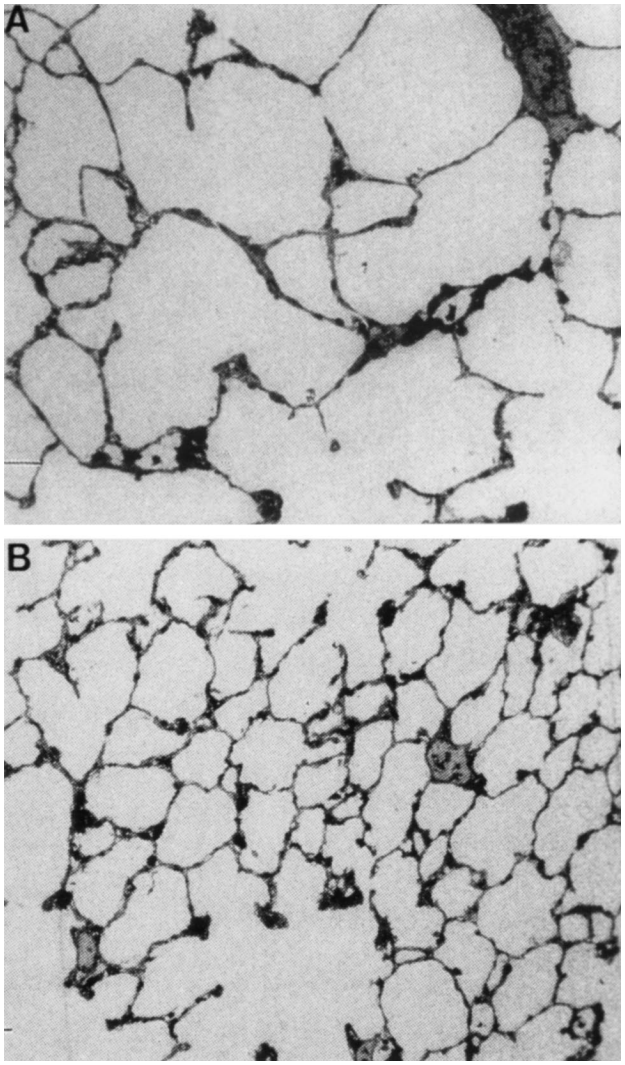

Fig. 3. Photomicrographs of rat alveoli after elastase administration (panel A) and after elastase followed by all-trans-retinoic acid (panel B). Note the severe emphysema in panel A and the remarkable preservation of alveoli in panel B. (From Reference 32, with permission.)

Small trials of retinoids in COPD patients have suggested a benefit to FEV_1 and tolerable adverse effects.[34] More importantly, the National Institutes of Health has been conducting the FORTE (Feasibility of Retinoic Acid Treatment in Emphysema) trial for the last several years. In that trial 300 emphysema patients were randomized to one of 4 regimens: high-dose retinoic acid (2 mg/kg/d), low-dose retinoic acid (1 mg/kg/d), 13-C retinoic acid, or placebo. Patients received the assigned regimen for 6 months and then crossed over for 3 months. The measured variables were pulmonary function testing, computed tomograms, quality-of-life scores, bronchoscopic markers of inflammation and repair, and pharmacokinetics. The last of these patients was enrolled in June 2002 and follow-up has been occurring since then. The data should be analyzed and released soon.

Should the FORTE trial be positive, larger trials will be required to confidently characterize the benefits and risks of retinoids for COPD. One thing that probably should be considered, however, is to use the aerosol route of admin-

istration. In rats the aerosol route produced significantly less systemic absorption, which should minimize adverse effects while producing a much longer half-life in alveolar tissue.[35]

Summary

As noted above, the best way to treat COPD is to prevent it in the first place. Unfortunately, as many as 10 million Americans have been unable to do that, and as a consequence, they have COPD. These patients experience disabling symptoms, high cost of care, and substantial mortality. Most current therapies are focused on symptom reduction and better disease management to avoid hospitalizations. Oxygen and, more recently, lung-volume-reduction surgery are the only modalities that have been shown to have a mortality benefit in selected patients.

A number of new approaches are being studied for COPD. Among these are 4 new approaches that are either in or close to phase III trials: long-acting bronchodilators, PDE4 inhibitors, vasodilators, and retinoids. Of those tiotropium appears to be the closest to receiving clinical approval in the United States, and its 24-hour duration of action should offer an important advancement in the care of these patients. The risk/benefit ratio and cost-effectiveness of the other compounds are less clear and await additional study. Further away are other approaches to managing COPD, including anti-oxidants, protease inhibition (and anti-protease stimulation), mucus regulation surfactants, and other ways of modulating the inflammatory process.[36,37] This is an exciting field and the need for better therapies is clear.

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Discussion

Shrake:* There is a shortage of respiratory therapists and there is a certain percentage of respiratory therapy that's overutilized, so there's a supply-and-demand gap, and my contention is that therapeutic modalities come and go, but the constant for the respiratory therapist—the factor that must always be there—is the ability to assess and treat and to be flexible in terms of the role you play. One of the things I talk about to groups of respiratory therapists is what would happen to your job if an effective bronchodilator regimen was created that allowed bronchodilation for 24 hours a day for 7 days or maybe even 30 days. The question is, what are the chances of that happening in the relatively near future? And, based on your answer, I believe the respiratory care profession would be at a crossroads in terms of closing that supply-and-demand gap and getting involved in other modalities that will make therapists even more effective members of the health care team in the future, such as administering nebulized aerosol for alveolar tissue repair. Or respiratory therapists could become a dying breed, so to speak. I vote for the former.

MacIntyre: Three of the 4 categories of therapies I discussed are going to require respiratory care expertise. Both of the long-acting β agonists and anticholinergics I discussed are given via inhalation, and I can't emphasize enough how important it is to do it right. These drugs are going to be expensive, and we must be sure we use them properly, with the proper techniques and the proper devices, which requires that people know what they're doing. The vasodilators—if you believe that NO or NO-like gases are going to be where the action is—are clearly going to require expertise, with mixing, preparing tanks and cylinders, and with delivery devices. With the retinoids, I think, to limit the potential toxicities, the aerosol route may well be the way to go, and we are going to need special devices and techniques to deliver retinoids. I think it's increasing the role of respiratory therapists, rather than decreasing it.

Wedzicha: This is how we use therapy in COPD. The example is a phosphodiesterase inhibitor, which works through an anti-inflammatory effect—if it works—by activating neutrophils, in which case we need to look for patients who have evidence of neutrophilic airway inflammation. I think one of the issues with clinical trials of COPD is that we have to include the target group. So with retinoic acid we look for patients with emphysema. With phosphodiesterase inhibitors we want to include the patients with airway inflammation, who have a lot of exacerbations.

MacIntyre: I couldn't agree with you more. I actually have more experience in sepsis trials, where I think that point is perhaps even more germane. Sepsis and acute respiratory distress syndrome trials are huge "wastebasket diagnoses" that encompass a variety of pathogenetic mechanisms, depending on the organisms, the host response, and the genetics. And these clinical trials sort of take everybody, and you may see a little overall effect in a subgroup. That "little" effect may well be because there are only certain subgroups in whom it really works. And that's a huge problem in clinical trials in general. I think it applies to these as well.

However, sometimes you can spend a lot of money, energy, and time trying to identify a particular patient, when it's cheaper to just go ahead and treat almost everybody. How rigorous you want to be in trying to find the appropriate subgroup can depend on

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the cost and toxicity of the drug. For instance, bronchoalveolar lavage and neutrophil analyses aren't very expensive, though they're not free either. But it's an issue in any clinical trial, identifying the subgroups that are responding when you take all comers, as we do when we use these "wastebasket diagnoses."

Enright: We've probably all been on a medical ward and seen a bright flash of light and a pop and some screwing around when someone lights up a cigarette while they're wearing oxygen. Clearly, people are excluded from receiving expensive and high-risk therapies such as lung transplants and LVRS if they are unable to stop smoking, and that's biochemically verified in most of these trials. What do you think about the less-expensive and lower-risk medications for patients who are unable to stop smoking? Do you think they should be excluded? For instance, a bronchodilator opens the airways and allows greater lung deposition of toxins and irritants from continued cigarette smoking.

MacIntyre: Cigarette smoking, unfortunately, as we heard yesterday from Scott Marlow,[1] is a very addictive habit. It's difficult to kick, even for patients who would really like to kick it. They are symptomatic from it. And, therefore, I'm not one to withhold things like bronchodilator therapy, or things that are not terribly expensive, such as pulmonary rehabilitation or oxygen therapy, from them because of it. There was a lot of argument with the Centers for Medicare and Medicaid Services as to whether you had to be off cigarettes before you got pulmonary rehabilitation. Mine was one of the institutions that said the only admission criteria is a desire to quit and to give it a shot, as opposed to actually having shown you can kick the habit. So I'm pretty comfortable treating patients if the drugs and therapies aren't terribly expensive or risky.

Having said that, I think we may have to draw a line somewhere with expensive or risky treatments such as lung-volume-reduction surgery, lung transplantation, and alpha-1 antitrypsin replacement. I don't know what will be the cost of the drugs I discussed. I don't think they're going to be as expensive as alpha-1 antitrypsin augmentation, but they're not going to be 5 cents a nebule, either. I think we're going to have to look at where to draw the line. But, clearly, the super-expensive and risky treatments ought to be reserved for patients who have optimized themselves, using all other modalities, including stopping smoking, before you give it to them.

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Hill: With regard to vasodilators and NO, back in the 1980s there was a lot of interest in using vasodilators for COPD. People were using what was available then.

MacIntyre: Such as almitrine?

Hill: Yes, and hydralazine and calcium channel blockers. Not only didn't they improve anything, but they often made oxygenation worse, although they did lower pulmonary vascular resistance. The difference with NO, of course, is that it has the potential of improving ventilation/perfusion matching while it lowers pulmonary vascular resistance. But, frankly, the changes you showed in that one study on hemodynamic effects aren't very impressive, because if FEV_1 is 500 mL before NO, it's probably still pretty close to that after NO. And physiologically, the major limitation is probably still going to be airway obstruction. So unless there's some reason to think that a minor decrease in pulmonary vascular resistance is going to help you functionally, I'm wondering whether we should have much optimism about vasodilation significantly improving functional capacity.

MacIntyre: I think the reason the current generation of pulmonary vasodilators is having more success than the drugs you just mentioned is because they focus on the pulmonary circulation. One of the big problems with the vasodilators back in the 1980s and even in the 1990s was that they caused systemic vasodilation as well, so systemic pressures would drop, mixed venous saturation would drop, and P_{O_2} could drop real fast.

Today's drugs are more focal in the lung and have less systemic effect, so the P_{O_2} effects are better than the old drugs. You mentioned that these changes are modest, and they certainly are. I'm not going to give everybody NO, of course, or NO analogues or prostacyclines, or endothelin antagonists. I think those drugs, even if they do prove valuable, are going to be primarily for pulmonary hypertension. This is not for everybody with COPD. It's going to be for people with substantial pulmonary hypertension.

We know pulmonary hypertension is an important marker of COPD mortality. I think one of the reasons the NOTT [Nocturnal Oxygen Therapy Trial] was positive was that P_{O_2} was made better, and pulmonary hypertension was probably made better. That's one of my interpretations of the NOTT. So I think if we focus in on that group, it goes back to Wisia's [Wedzicha] point about identifying very specific people in whom pulmonary vascular resistance is high and causing substantial symptoms and putting them at high risk for mortality. That's where I would limit it.

Fahy: At the European Respiratory Society meeting in Madrid, I remember someone talking about retinoids, and he didn't think (based on studies using rats) that retinoids are going to be a great success in humans, because the rat lung continues to regenerate throughout the rat's life and humans stop regenerating at about age 6. There are humans who are "rats," but their lungs don't act the same way. Do you have any comments, not on humans being rats, but on the prospect of regeneration of lung tissue?

MacIntyre: You're absolutely right. That's why the FORTE trial was conducted. There's enough animal data out there, but humans are not rats, sheep, or pigs. Each species might respond differently. The rat is an exquisitely beneficial model to demonstrate alveolar regeneration because it *does* have the properties you described. Nevertheless, retinoids do work in other human systems, for instance in skin interstitium and other human tissues. I think that evidence makes it worth doing the trial. But your point is well taken. When the FORTE report comes out and my retinoid discussion has shrunk considerably, it's because what you just said is true.

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