New Insights Into the Temporal Pattern of Hypoxemia in COPD

The life-preserving benefits of long-term oxygen therapy (LTOT) were established nearly 2 decades ago. One cannot overemphasize the fact that LTOT is the only treatment that has a positive impact on mortality in COPD patients. Pulmonologists are well versed in the benefits of LTOT, and recognize the importance of identifying hypoxemic patients and instituting LTOT. The criteria for implementation of LTOT are well defined. Therefore, it is somewhat surprising that there has been little interest in building on the findings of the original studies that documented the survival benefit of LTOT. Acceptance of LTOT has lead to a complacency that there is nothing more to learn on this topic, especially in the molecular biology era.

The limitations of the original studies on LTOT are not widely appreciated. Some very interesting questions remain unanswered. The answers could have a major impact on the effectiveness of LTOT. For example, the original studies provided little insight into the frequency and magnitude of hypoxemia in COPD patients in the outpatient setting. Oximetry was not widely available, and arterial blood samples were drawn at infrequent intervals in the hospital or clinic setting. The article by Plywaczewski et al (March 2000) is a good example of the renewed interest in questions related to gaps in knowledge about adequate oxygenation in the outpatient setting. This report is the latest work from these authors focused on nocturnal oxygen desaturation in COPD patients. The results provide new data relevant to an unresolved issue: the frequency and magnitude of nocturnal oxygen desaturation in these patients. This study demonstrates a higher frequency of nocturnal desaturation than in prior work, suggesting that we may be underestimating the frequency and magnitude of nocturnal desaturation. Although this work does not completely resolve this issue, the results provide additional support for the American Thoracic Society recommendation that clinicians increase the liter flow of oxygen during sleep in COPD patients to avoid nocturnal desaturation.

Other reports indicate that unanswered questions concerning LTOT are beginning to receive more careful scrutiny. Several studies demonstrated that the frequency and magnitude of hypoxemia in COPD patients in the outpatient setting is greater than anyone previously realized. These studies herald the emergence of a new field, the monitoring of oxygen saturation (and other physiologic variables) in the outpatient setting, set in motion by earlier work. This is an interesting development, because this approach should provide a more accurate picture of the temporal profile of oxygen saturation (or desaturation) while patients with advanced lung disease are engaged in activities of daily living. This approach is linked to the continued improvement in monitoring equipment that will facilitate the assessment of physiologic variables in the outpatient setting. Outpatient monitoring could eventually replace the current type of evaluation for LTOT, which does not reflect patient activity outside of the hospital or clinic.

Why is this important? Our goal is still to reduce the morbidity and mortality in patients with COPD. Defining the temporal profile of oxygen saturation during activities of daily living may enable us to optimize LTOT beyond the level in the original studies. This is certainly relevant to the issue of nocturnal desaturation highlighted by Plywaczewski et al. A challenging long-term objective will be to demonstrate that optimizing LTOT with outpatient monitoring leads to improved outcomes in patients with advanced lung disease. Can we achieve even better survival rates than in the original studies on LTOT using data derived from outpatient monitoring? This is not an unreasonable hypothesis in view of findings of one study that untreated exercise-induced hypoxemia worsens survival in COPD. Increased life expectancy in the general population will lead into an increase in the numbers of patients surviving beyond age 70 with chronic diseases, like COPD. Therefore, reducing the morbidity and mortality in patients with advanced lung disease will take on added significance. Developing new ways to optimize LTOT fits well with these objectives. This is
the broader context in which the results of Plywaczewski et al. should be considered.

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REFERENCES

Spironolactone for Heart Failure

Spiraling Out of Control

Pharmacologic treatments improve survival and quality of life in patients with heart failure. Angiotensin-converting enzyme (ACE) inhibitors are well documented to improve both of these outcomes. The judicious use of β-blockers reduces mortality in patients with New York Heart Association (NYHA) class II and III symptoms. Although digoxin does not reduce all-cause mortality, it does reduce morbidity. More recently, a large clinical trial, the Randomized Spironolactone Evaluation Study (RALES), demonstrated that an old drug, spironolactone, administered in low doses, also improves survival. We worry that this result, from this single trial, has been embraced with undue enthusiasm and applied indiscriminately to patients with all classes of congestive heart failure (CHF), rather than to patients similar to those studied in the trial. In addition, we are concerned that CHF patients treated with spironolactone do not have their diuretic, β-blocker, and ACE inhibitor regimens optimized, nor are they being followed up carefully to look for electrolyte abnormalities, such as hyperkalemia and azotemia, sometimes caused by spironolactone. The simplicity of administering spironolactone therapy, compared with the work involved in titrating doses of ACE inhibitors and β-blockers, has only increased enthusiasm for this drug.

A careful review of the patients and the protocol of RALES is in order here. Patients were eligible for study if they were in NYHA class IV heart failure within 6 months of enrollment and if they had NYHA class III and IV symptoms at enrollment. In addition, those eligible had a measure of left ventricular ejection fraction no greater than 35% and a serum creatinine level of ≤ 2.5 mg/dL. Almost all enrolled patients were being treated with ACE inhibitors and loop diuretics. Thus, the patients enrolled in RALES had severe symptoms due to left ventricular dysfunction, despite treatment with loop diuretics and ACE inhibitors.

Patients enrolled in RALES received either placebo or spironolactone; all patients receiving spironolactone were randomized to receive 25 mg po qd. All patients received very close follow-up:

- Laboratory assessment at 1 week.
- Clinical follow-up and laboratory assessment at 4 weeks.
- Laboratory assessment at 5 weeks.
- Clinical follow-up and laboratory assessment at 8 weeks and 12 weeks, then every 3 months for up to 1 year, then every 6 months thereafter. Of note, patients who did not develop hyperkalemia continued to receive spironolactone, 25 mg/d po, for at least 8 weeks, before a dose increase to 50 mg po qd was considered. This was then instituted for patients with signs and symptoms of progression of heart failure despite receiving 25 mg/d spironolactone. Laboratory results were again checked 1 week after the dose increase.

We want to emphasize that patients in RALES received no more than 25 mg/d or 50 mg/d total...