How (Why) Does Oxygen Work in Advanced COPD?

Long-term oxygen therapy (LTOT) is established as the standard of care for selected patients with advanced chronic stable hypoxemia. A large body of scientific evidence, including two well-defined and well-conducted controlled clinical trials, shows that oxygen has a survival benefit. In the Nocturnal Oxygen Therapy Trial (NOTT), survival was better in patients who received ambulatory oxygen therapy compared with those assigned to receive oxygen from a stationary source. However, the mean duration of the oxygen therapy was greater for ambulatory oxygen (17.7 vs 11.8 h per day, respectively) than in those assigned to nocturnal and stationary oxygen. Thus, the difference in survival could be due to the duration of oxygen therapy, the method (ie, ambulation), or both.

It is interesting that in the British Medical Research Council study, the survival benefit did not appear for 500 days. In the NOTT study, statistical survival differences compared to continuous oxygen therapy compared to nocturnal oxygen therapy did not become statistically significant until after 3 years. Why the delay?

O'Donohue has argued in favor of the “restorative” effect of oxygen. A short explanation of the thesis of the late Walter O'Donohue is that oxygen somehow restores ventilation perfusion matching in the lung, resulting in normoxemia in patients who previously had chronic stable hypoxemia. These patients did not experience any improvement in lung mechanical function during the follow-up. This is a quite different matter than when LTOT is prescribed following exacerbations of COPD. Many of these individuals have an improvement in lung function and may not be candidates for LTOT on full recovery.

I have long argued for another NOTT study to compare outcomes in terms of survival, number of exacerbations, quality of life, and the economics of continuous oxygen therapy, using a modern ambulatory system carried by the patient weighing less than 5 lbs compared with stationary oxygen therapy. New technologies now allow this. If a survival benefit can be traced to ambulatory oxygen, the question will be how and why. Answers must be sought at the molecular cellular level. Does continuous oxygen therapy counter the adverse effects of “hypoxia genes.” Does ambulatory oxygen improve energy production at the tissue level better than when stationary oxygen therapy is used?

The length and quality of life has improved for COPD patients over the past 30 years. Part of this improvement can be assigned to better pharmacologic therapy and to the widespread use of LTOT. COPD patients can now live into their 70s and 80s. Today, some 1 million people with COPD and related disorders receive oxygen therapy, and approximately 70% of them are assigned to a stationary system, a largely arbitrary decision made through a lack of knowledge of the available technologies by prescribing physicians or for economic considerations of suppliers.

We badly need the answers to how and why oxygen works in patients with chronic stable hypoxemia in the present era. Prospective controlled clinical trials conducted with a sufficient number of patients to achieve a clear-cut outcome should be an extremely high priority for funding agencies.

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Is a Charge a Cost If Nobody Pays It?

Aproximately one third of patients undergoing coronary artery bypass graft surgery will develop atrial fibrillation (AF). AF is more common in elderly patients and those with COPD or hypertension. Its occurrence, and particularly its recurrence, were associated with encephalopathy, strokes, renal dysfunction, infection, in-hospital deaths, more use of CT scans and noncardiac ultrasomography, and longer ICU and hospital stays. However, patients with AF were less likely to have myocardial infarctions or congestive heart failure, and they underwent fewer echocardiograms and EEGs. Additionally, AF is a risk factor for late mortality.

While a variety of medicines, including amiodarone, have been shown to decrease the occurrence of AF, disagreement persists about the cost benefits of prophylaxis with amiodarone. Daoud et al. using the sum of direct variable, fixed direct costs, and indirect costs, found that amiodarone prophylaxis decreased hospital costs by $8,161 per patient. In a mathematical modeling exercise using departmental cost/charge ratios and physician work relative value units, Mahoney et al. claimed that the use of IV amiodarone for universal prophylaxis in patients undergoing coronary artery bypass graft surgery would increase in-hospital costs by $24,934 for each episode of AF prevented. Other studies, using a variety of analyses, have found no difference in costs between groups receiving amiodarone and control groups. Into this controversy step Kerstein et al. (see page 716) with a novel and convenient method for administering amiodarone that decreased the incidence of AF from 26 to 6%. Given the association between AF and morbidity and mortality, the authors should be encouraged to perform a randomized, double-blinded, placebo-controlled study of amiodarone and AF. The authors also report that universal prophylaxis is very cost-effective, saving $1,242 per treated patient. However, the authors do not determine the cost. They multiplied the average length of hospital stay by a constant charge per day to arrive at a total “cost.” There are three main problems with this, as follows: (1) length of stay correlates poorly with direct variable cost after cardiac surgery; (2) most of a hospital charge consists of fixed or indirect costs that are not saved by preventing AF; and (3) their calculation does not capture any costs related to the adverse effects of amiodarone. Only if the use of amiodarone increases length of stay is it recognized as a cost. Amiodarone can cause pulmonary infiltrates, thyroid dysfunction, heart block, and ventricular dysrhythmias. In this length of stay-based accounting system, all extra tests and procedures related to the adverse effects of amiodarone have no cost. They are free, which is obviously not correct.

Then how shall we determine the costs or savings of using amiodarone to prevent AF? Cost studies are usually divided into the following four types: cost-minimization; cost-benefit; cost-utility; and cost-effectiveness. Cost-minimization studies compare two or more equally efficacious therapies to determine which is the least expensive. Cost-benefit studies necessitate converting all outcomes (eg, pain, emesis, renal failure, myocardial infarction, and death) to a monetary value. Cost-utility studies determine the cost of a utility metric, such as $10,000, for each quality-adjusted year of survival. Cost-effectiveness studies determine the monetary cost of preventing unwanted outcomes (eg, death, ventilated associated pneumonia, and AF). Recommendations on conducting cost-effectiveness studies have been promulgated by the US Public Health Service and the European Society of Intensive Care Medicine. We would use a cost-effectiveness study to determine the monetary cost for each case of AF prevented. The results can range from negative cost (ie, amiodarone use saves more money than it costs, as found by Kerstein et al), to positive cost (ie, amiodarone use increases costs but at least prevents AF), to infinite cost (ie, amiodarone use costs more and does not prevent AF). Next, we would determine whose perspective is determining cost. The view can be that of the hospital, the insurance company, the patient, or the society. They are not interchangeable. An action that reduces hospital cost, such as early hospital discharge, may increase the cost to the patient or insurance company by, for example, the need to pay for home health care or a stay at an extended-care facility.

But what is a cost? Problems arise when costs and charges are used synonymously. At my hospital, I frequently see sales representatives who compare the purchase price of their item to the hospital...