CHEST

POINT:

Does Low-Dose Oxygen Expose Patients With COPD to More Radiation-Like Risks Than Patients Without COPD? Yes

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ABBREVIATIONS: AOT = ambulatory oxygen therapy; BTS Home Oxygen Guidelines = British Thoracic Society Guidelines for Home Oxygen in Adults; CH = chronically hypoxemic; LDO = low-dose oxygen; LDOT = low-dose oxygen therapy; LFOT = low-flow oxygen therapy; LOLA = lowest oxygen level acceptable; LTOT = long-term oxygen therapy; MRC = Medical Research Council; NAC = N-acetyl-cysteine; NC = nasal cannula; NOTT = Nocturnal Oxygen Therapy Trial; OT = oxygen toxicity; ROIH = radiation-oxygen injury homology; RONS = reactive oxygen and nitrogen species; Spo_2 = oxygen saturation by pulse oximetry

We argue that low-dose oxygen therapy (LDOT) *does* expose patients with COPD to more radiation-like risks than patients without COPD. Three considerations subtend our assertion: radiation and oxygen share oxidative stress mechanisms that constitute radiation-oxygen injury homology (ROIH); patients with COPD have higher, more problematic exposure rates to LDOT vs patients without COPD; and patients with COPD vs patients without COPD have disease burdens that amplify ROIH from LDOT. Thus, LDOT, independent of benefits, poses radiation-like risks with pernicious results that follow stochastic patterns.[1,2]

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We use LDOT, low-flow oxygen therapy (LFOT), and long-term oxygen therapy (LTOT) as synonymous terms throughout this article.

Scope of the Problem

COPD arises when oxidative stress in susceptible individuals manifests as structural and functional failures with clinical manifestations that ramify along a biopsychosocial continuum.[3] Implicitly, the Global Initiative for Chronic Obstructive Lung Disease, the American Thoracic Society-European Respiratory Society, and the American College of Physicians COPD classifications and treatment guidelines endorse this perspective.[4]

In 2013, the Centers for Disease Control and Prevention reported 6.4% of US adults (about 15.7 million adults) were "told" by *any* health professional that they had COPD. Further, 22.1% of patients with COPD (vs 6.7% of those without) used "special equipment to manage health problems," without specifying LDOT devices.[5] These Centers for Disease Control and Prevention data do not offer a granular view of LDOT use.

Nishi et al,[6] using Medicare Parts A and B records, showed that *any* oxygen use among COPD beneficiaries rose from 33.7% in 2001 to 40.5% in 2010, whereas sustained oxygen use varied from 19.5% in 2001 to 26.9% in 2008 when service reimbursement formulae changed, before dropping to 18.5% in 2010. These data endorse problematic LDOT use influenced by sociopolitical factors. They also found LDOT was highest among non-Hispanic, white women with two or more comorbidities and low socioeconomic status, engendering questions about the applicability of classic LDOT life extension studies to this population. Further questioning the applicability of these studies to other populations is appropriate.[7]

Sources of ROIH

ROIH was first recognized more than 70 years ago.[8] In 1934, de Almedia noted histological homologies in x-irradiated and hyperoxia-exposed testes. Gerschman, in 1954, postulated free radicals as the "…common mechanism between oxygen poisoning and x-irradiation…." In 1962, Noell, studying vision, noted that cumulative "oxygen poisoning" resembles "x-irradiation effects." Gilbert, in 1972, reiterated that radiation catalyzes

oxygen toxicity. Mensel, in 1970, underscored that ozone—an oxygen allotrope—causes radiation-like damage. Microbiologists postulate that radiation resistance via antioxidant-like mechanisms developed before atmospheric oxygen accummulated.[9] That free radicals and reactive oxygen species cause molecular and submolecular damage and govern multiple, often competing translational/transcriptional events, is axiomatic.[10] Regression analysis shows not smoking and lower atmospheric oxygen tension secondary to higher elevation as inverse predictors for lung cancer.[2]

Figure 1 depicts ways ROIH can incite cellular injury. Oxygen partial pressure variations from evolutionarily determined (physoxic) levels produce adaptive and pathological responses.

Electrons (e^-) and reactive oxygen and nitrogen species (RONS) that generate free radicals are ROIH common denominators.[11,12] Hydroxyl radicals, hydrogen peroxide, superoxide, and singlet oxygen species produced by oxidative phosphorylation and nonrespiratory enzymatic and nonenzymatic oxygen activation have parallels in water irradiation. These moieties react with nitric oxide to produce RONS such as peroxynitrite, which also cause injury and/or translational/transcriptional events that reset homeostasis.

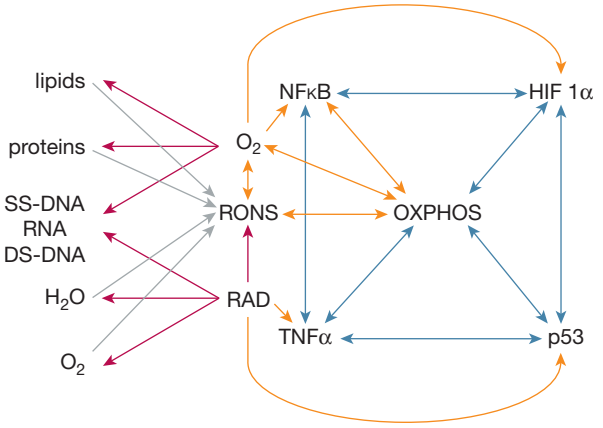

Figure 1 – *Pro-oxidant effects of radiation (RAD) and oxygen (O_2) produce reactive oxygen and nitrogen species (RONS) that cause direct molecular and submolecular injury with lipid, protein, and nucleic acid structural consequences; RONS also participate in transcriptional/translational events that reset homeostasis. Oxidative phosphorylation (OXPHOS) exerts its powerful influence on RONS generation, antioxidant level control (not shown), and codon and gene product activation, especially hypoxia inducible factors (HIF-1), nuclear factor kappa B (NFκB), protein 53 (p53), and tumor necrosis factor alpha (TNFα). Antioxidants regulate and counterregulate pro-oxidant effects to produce "molecular whiplash" because antioxidants may become reactive species in and of themselves. Because mitochondria are primary RONS sites, mitochondrial genomes are more susceptible to injury than nuclear genomes because of proximity and marginal protection/repair mechanisms, which is only compensated for by heteroplasmy. DS-DNA = double-stranded DNA; SS-DNA = single-stranded DNA.*

Regarding ionizing radiation, health professional and consumer concerns about medical imaging radiation exposure risks, especially in children, reflects both postulated and proven harm. The US government and medical societies recommend "radiation reduction" strategies such as "as low as reasonably achievable" (ALARA), also reflected in The American Board of Internal Medicine Foundation's "Choosing Wisely" campaign. To date, oxygen has escaped equivalent attention, though risk awareness is increasing.[13] Notably, the Occupational Safety and Health Administration and Food and Drug Administration regulate oxygen, depending on intended use, industrial or medical, respectively.

Patients With COPD Have Problematic LDOT Exposures

Our review suggests that patients with COPD have (1) higher exposure rates to LDOT/LFOT/LTOT and (2) more problematic exposures than patients without COPD.

Our PubMed search using "low-dose oxygen therapy for COPD patients" and "low-dose oxygen therapy for non-COPD patients" for LDOT; "low-flow oxygen therapy for COPD patients" and "low-flow oxygen therapy for non-COPD patients" for LFOT; and "long-term oxygen therapy for COPD patients" and "long-term oxygen therapy for non-COPD patients" for LTOT is summarized in Table 1. We were surprised by the paucity of results for all search terms, particularly LDOT and LFOT.

In 2000, Zieliński noted no controlled trials assessed LTOT in patients without COPD comparable to the Nocturnal Oxygen Therapy Trial or the British Medical Research Trial, two acknowledged 1980s trials still used to model life-saving COPD oxygen therapy.[14] He catalogued COPD/non-COPD LTOT use in seven different countries finding variations from 39%/61% in Japan to 93.4%/6.6% in the Czech Republic. In the United States, where about 80% of LTOT users are Medicare recipients, rates were 76%/24% COPD/non-COPD. The non-COPD pulmonary conditions associated with LTOT were tuberculous sequelae, interstitial pulmonary fibrosis, pneumoconiosis, kyphoscoliosis, bronchiectasis, and cystic fibrosis; in children, these were restrictive lung disease conditions associated with neuromuscular disease and bronchopulmonary dysplasia. Although these conditions share oxygen use with COPD, none evince the total COPD pathophysiologic spectrum. Cystic fibrosis, OSA, and pulmonary hypertension associated with COPD and congestive heart failure constitute other LTOT populations.