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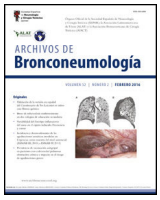

Editorial

When and When Not to Prescribe Home Oxygen in COPD

Long-term oxygen therapy (LTOT) may prolong life of patients with chronic obstructive pulmonary disease (COPD) in very specific circumstances.[1,2] However, the benefits of oxygen come at a price. It is inconvenient and expensive. It has a negative impact on patient's self-image, interferes with activities and is associated with poor quality of life.[3,4] The prescription of oxygen therapy hence marks an important step in the course of the disease. In this clinical note, our objectives are to increase clinicians' awareness to the current indications and prescription practices in COPD, to underline the limitations of their scientific foundation and to introduce the concept of "precision medicine" in the field of home oxygen therapy.

Prescription practices: starting patients on oxygen

Most patients with COPD who receive LTOT were started on oxygen during the course of an exacerbation complicated by severe hypoxemia, often at hospital discharge. The prescription of oxygen is then a matter of safety. This prescription is temporary and usually referred to as "short-term oxygen therapy" (STOT). Clinicians will then usually apply the same prescription criteria as for LTOT ($PaO_2 \leq 55$ mmHg at rest, or a $PaO_2 < 60$ mmHg with evidence of cor pulmonale or erythrocytosis),[1,2] although these criteria for STOT are not based on evidence.

Close follow-up of patients just started on home oxygen is mandatory. Half will remain severely hypoxemic after repeated arterial blood gas measurement at 3-month follow-up and will require that supplemental home oxygen be continued.[5] STOT then becomes LTOT. Oxygen will be discontinued in the others after PaO_2 improved to the point that it exceeds the criteria for LTOT prescription. Unfortunately, formal reassessment of these patients is often overlooked. This situation has been identified by the Choosing Wisely initiative as one of the top five areas of improvement in adult pulmonary medicine.[6] It is during this re-evaluation that very important decisions are made, usually on the basis of PaO_2 measurement and prescription thresholds set by the Nocturnal Oxygen Therapy Trial (NOTT) and the British Medical Research Council (BMRC) trial.[1,2] Although simple and convenient, the practice of arterial blood measurement has its own limitations since it represents a static and instantaneous measure that may not reflect patients' long-term oxygenation status. Nevertheless, direct measurement of PaO_2 has the merit to conform with the evidence that is currently available.

Limitations of the current prescription thresholds

The perceived benefits of home oxygen are usually undisputed when very severe hypoxemia is noted. Several areas of uncertainty remain however. This uncertainty is from the definitions of "severe hypoxemia" and "moderate hypoxemia" that have not been well validated.[7] The threshold of $PaO_2 \leq 55$ mmHg was chosen by the NOTT investigators following the observation that tissue hypoxia is noted when PaO_2 approximates 50 mmHg.[8] Physiological responses to hypoxia vary among populations and individuals, and the phenomena of adaptation and tolerance to hypoxemia/hypoxia exist.[9] The true benefits of home oxygen may be marginal, especially when PaO_2 approximates 55 mmHg in the absence of early or late end-organ dysfunction. On the contrary, end-organ dysfunction may be noted when hypoxemia is only moderate.[10,11] In these circumstances, the effects of supplemental oxygen is uncertain since patients with end-organ dysfunction were under-represented in the randomized trials conducted so far. Otherwise, home oxygen has no significant effect on survival when hypoxemia is moderate and uncomplicated.[12]

Chronic hypercapnia

Another observation from the NOTT and the BMRC trial is that hypercapnia may determine response to LTOT. Patients enrolled in the BMRC trial were severely hypercapnic; mean $PaCO_2$ was 53–55 mmHg, indicating significant respiratory insufficiency among participants.[2] In the NOTT, mean $PaCO_2$ was normal (43–44 mmHg).[1] In a subgroup analysis, no difference in mortality was seen among those with normocapnia, whereas the largest differences in mortality were noted in those with hypercapnia and respiratory acidosis at baseline. The benefit of LTOT in normocapnic patients is therefore unknown.

End-organ dysfunction

Both the NOTT and the BMRC trial included patients with late end-organ dysfunction. In the NOTT, it is only after 5 months of poor recruitment (24 patients randomized) that the investigators expanded the inclusion criteria to enroll patients with a PaO_2 in the range of 56–59 mmHg with evidence of cor pulmonale or severe erythrocythemia (hematocrit $\geq$ 55%).[13] This additional set of criteria concurred with those of the BMRC trial that required that patients be admitted only if they had one or more recorded episodes of heart failure.[2] Cerebral dysfunction may also complicate chronic hypoxemia in COPD.[14] Overt end-organ

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dysfunction indicates that chronic hypoxemia is significant and deleterious. However, end-organ dysfunction represents very late consequences of chronic hypoxemia.

Earlier (preclinical) markers of adaptation (or maladaptation) to chronic hypoxemia would be useful to predict outcomes and to decide whether home oxygen is truly indicated. In normal individuals exposed to hypoxic conditions, the accumulation of hypoxia-inducible factors (HIF) in the cell nucleus up-regulates several target genes responsible for physiologic responses to hypoxia including remodeling of the pulmonary vasculature leading to pulmonary arterial hypertension and increased erythropoiesis.[15] HIF, erythropoietin and vascular endothelial growth factor (VEGF) have been identified as potential serum markers of hypoxemia that could be used clinically to identify the impact of supplemental oxygen upon repeated measures.[16] HIF signaling, however, is not fully understood in COPD and mixed results have been reported.[17,18] Another marker of chronic hypoxemia in COPD that appears early in the course of the disease is microalbuminuria that may indicate increased cardiovascular risk.[19]

Precision medicine is the future

LTOT is not a panacea. In the BMRC trial, 500 days elapsed before the effect of LTOT on survival appeared, when compared to no oxygen therapy.[2] At 5-year follow-up, those who received oxygen had improved survival: 42% had died, compared to 66% of those in the control group. The difference (24%) corresponds to a number needed to treat (NNT) of 5 (five patients must receive oxygen during 5 years in order to prevent one death over this period). In the NOTT, NNT was 6 at 24-month follow-up.[1] If LTOT benefited to all severely hypoxemic patients, NNT would be 1.

It is therefore the physician's responsibility to carefully target the right treatments to the right patients at the right time. This is the principle of "precision medicine" sometimes known as "personalized medicine" or "stratified medicine". It represents an innovative approach to tailoring disease prevention and treatment that takes into account differences in individual clinical, genetic, environmental, lifestyle and biomarker information.[20] Only a better understanding of the mechanisms of chronic hypoxemia and its management will make precision medicine possible in the field of oxygen therapy.

Current recommendations

Current knowledge from randomized trials still indicates that patients with severe hypoxemia ($PaO_2 < 60$ mmHg) complicated by end-organ dysfunction and/or hypercapnia are likely to benefit from LTOT. LTOT is then expected to improve survival. The evidence to support LTOT when severe hypoxemia is noted without end-organ dysfunction or hypercapnia is much less compelling. Its prescription should be the result of a shared-decision process. Patients with moderate hypoxemia should not be offered LTOT without evidence of end-organ dysfunction. Finally, LTOT may be considered in the rare occurrence of moderate hypoxemia complicated by end-organ dysfunction, although evidence from clinical trials is lacking. New data from cohort studies are needed to better stratify patients according to the likelihood of benefit from home oxygen therapy.

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Conflicts of interest

None declared.

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