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Supplemental Oxygen Therapy in Medical Emergencies: More Harm Than Benefit?

In medical emergencies, such as acute coronary syndrome, cardiopulmonary resuscitation (CPR), stroke, and exacerbations of chronic obstructive pulmonary disease (COPD), supplemental oxygen is often routinely administered. Most physicians believe this intervention is potentially lifesaving, and many guidelines support the routine use of high-dose supplemental oxygen.

Over the decades, however, potential detrimental effects of supplemental oxygen appear to have been ignored. Many clinicians are unaware of the variety of preclinical studies that have been executed, showing that hyperoxia causes both coronary and systemic vasoconstriction, resulting in deterioration of several important (hemodynamic) parameters (**Table**). The prime candidate mechanism for these unintended effects is believed to be the formation of reactive oxygen species. In this Research Letter, we draw attention to the collective clinical evidence, which argues against the routine use of high-dose oxygen. Awaiting more thorough studies, we strongly recommend a policy of careful, titrated oxygen supplementation.

Methods. We conducted a search of the literature in MEDLINE and EMBASE to identify articles addressing the effect of oxygen therapy in acute coronary syndrome, cardiopulmonary resuscitation, stroke, and exacerbations of chronic obstructive pulmonary disease.

Results. Large (randomized) clinical studies addressing oxygen supplementation are scarce. In 1976, a double-blind randomized trial was performed in 200 patients with suspected acute myocardial infarction. In the supplemental oxygen group, 9 of 80 patients (11%) died, as opposed to 3 of 77 (3.9%) in patients breathing compressed air (relative risk [RR] of mortality, 2.9; 95% CI, 0.8-10.3). A recent Cochrane review combined this trial with a smaller similar one, which generated a composite RR of mortality of 3.03 (95% CI, 0.93-9.83).[1] In acute decompensated heart failure, no clinical studies are available, despite the rather abundant evidence from preclinical studies, suggesting that such patients may experience the adverse effects caused by coronary and systemic vasoconstriction (Table).

In accordance with existing guidelines, supplemental oxygen is often administered during CPR. In the postresuscitation phase, evidence exists that 30% oxygen is more brain protective than pure oxygen.[2] Recently, an observational study in 6326 patients showed that supplemental oxygen induced postresuscitation hyperoxia was independently associated with increased mortality (odds ratio [OR], 1.8; 95% CI, 1.5-2.2). A subsequent analysis of the same cohort indicated that each 25–mm Hg increase in PaO_2 was associated with a sta-

Table. Effects of Supplemental Oxygen in Different Clinical Conditions

Clinical Condition	Effect Parameter	Effect	Reference
Exercise testing	ECG alterations	Prolonged	*JAMA*. 1950;144:373-375
Post myocardial infarction	Heart rate	Decreased	*Lancet*. 1964;2(7364):825-832
	Stroke volume	Decreased	*Br Heart J*. 1965;27:401-407
	Cardiac output	Decreased	*Br Med J*. 1968;4(5627):360-364
	Systemic vascular resistance	Increased	
	Mean arterial pressure	Increased	
Acute myocardial infarction	Vascular resistance of LAD	Increased	*J Appl Physiol*. 2007;102(5):2040-2045
Cardiac catheterization	Coronary vascular resistance	Increased	*Am J Physiol*. 2005;288(3):H1057-H1062
	Coronary blood flow	Decreased	
Congestive heart failure	Stroke volume	Decreased	*J Am Coll Cardiol*. 1996;27(2):353-357
	Heart rate	Decreased	*Am J Physiol Heart Circ Physiol*. 2002;282(6):H2414-2421
	Cardiac output	Decreased	*Chest*. 2001;120(2):467-473
	Systemic vascular resistance	Increased	*Heart*. 2010;96(7):533-538
	LV end diastolic pressure	Increased	
	Isovolumetric relaxation time	Increased	
COPD	Hypercapnia	Increased	*Clin Med*. 2002;2(5):449-451
	Mortality	Increased	*BMJ*. 2010;341:c5462
Stroke	Stroke severity score	Increased	*Stroke*. 2003;34(2):571-574
	Mortality	Increased	*Stroke*. 1999;30(10):2033 – 2037 NCT00414726[a]
Cardiopulmonary resuscitation	Neuron-specific enolase	Elevated	*Resuscitation*. 2006:69(2);199-206
	Mortality	Increased	*JAMA*. 2010;303(21):2165-2171 *Circulation*. 2011;123(23):2717-2722 *Critical Care*. 2011;15(2):R90

Abbreviations: COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; LAD, left anterior descending coronary artery; LV, left ventricular.
[a]Trial was terminated (Clinical Trial of Normobaric Oxygen Therapy in Acute Ischemic Stroke, not published, clinicaltrials.gov Identifier: NCT00414726).

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tistically significant 6% increase in the relative risk of death.[3] Finally, a comparable cohort of 12 108 patients was analyzed in New Zealand and Australia. Again, the hyperoxia group showed an increased risk of mortality compared with the normoxia group (OR, 1.2; 95% CI, 1.1-1.6). Although the statistical significance of this finding was not maintained after multivariable adjustment, certainly no beneficial effects of hyperoxia were found.[4]

In the management of ischemic stroke, a randomized trial suggested that hyperbaric oxygen may adversely affect stroke severity.[5] With regard to normobaric oxygen, 3 randomized trials were performed. One showed no benefit on clinical outcome.[6] Another trial in nonhypoxic patients found lower survival at 1 year (OR, 0.45; 95% CI, 0.23-0.90) in those who received supplemental oxygen during initial treatment.[7] The third randomized trial was terminated in 2009 after enrolling 85 patients because of excess mortality in the hyperoxia group (40% vs 17% [P=.01 by our own calculation]) (Clinical Trial of Normobaric Oxygen Therapy in Acute Ischemic Stroke [not published]; clinicaltrials.gov Identifier: NCT00414726). Although an external monitor judged the excess mortality as "unrelated to oxygen treatment," these results are important because this was the largest randomized trial investigating oxygen treatment for ischemic stroke, and it is remarkable that these results have not (yet) been published.

In the management of COPD, the risks of oxygen supplementation are widely acknowledged. Administration of oxygen in patients with COPD may cause hypercapnia due to ventilation-perfusion mismatching, the Haldane effect, inhibition of hypoxic drive, and atelectasis. Guidelines recommend a maximum FIO_2 of 0.28. However, patients with COPD often receive higher doses, especially during ambulance transportation, causing hypercapnia and increased mortality. Recently, a randomized trial compared high concentration oxygen with titrated oxygen in prehospital patients with exacerbation of COPD. Mortality was lower in patients receiving titrated oxygen (RR, 0.42; 95% CI, 0.20-0.89). In those with later-confirmed COPD, mortality reduction was even stronger (RR, 0.22; 95% CI, 0.05-0.91).[8]

Comment. In conclusion, there appear to be potential dangers of routine administration of supplemental oxygen during a variety of medical emergencies. Hyperoxia is associated with hemodynamic alterations that may increase myocardial ischemia and impair cardiac performance, and the results from relatively unknown preclinical studies appear to be supported by the available clinical evidence. Moreover, hyperoxia also seems to be associated with adverse outcomes in different noncardiac emergencies. Finally, in our extensive literature review, we did not find a single study contradicting the reported hazards of hyperoxia or, in fact, suggesting benefits.

We acknowledge that additional clinical research is warranted to determine whether routine high-dose supplemental oxygen in medical emergencies indeed causes more harm than benefit. Until that time, however, we call for appropriate caution in applying supplemental oxygen. Hypoxemia should be treated carefully with stepwise increases in inhaled oxygen concentration in an attempt to avoid arterial hyperoxia.

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Necessity for Primary Care Immediately After the March 11 Tsunami and Earthquake in Japan

On March 11, 2011, Japan was devastated by a massive magnitude 9.0 earthquake and tsunami. Immediately after the earthquake, the rescue of injured people was the most urgent task. However, a critical feature of this tragedy was that because

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