





David Aguilar<sup>1</sup> and Vijay Nambi<sup>2,3</sup>

## Taking the Air Out of Oxygen Supplementation in Individuals With Diabetes and Acute Coronary Syndromes

Diabetes Care 2019;42:2019-2021 | https://doi.org/10.2337/dci19-0035

Oxygen supplementation has been a cornerstone in the initial treatment of individuals with acute coronary syndrome. While consensus for oxygen supplementation exists for patients with hypoxia, oxygen supplementation has also been routinely used in those presenting with acute myocardial infarction (MI) with normal oxygen saturations based on the rationale that oxygen therapy could improve oxygen supply to the ischemic myocardium, thereby reducing the infarct size and complications. Indeed, reports of oxygen supplementation to relieve angina pectoris were described as early as 1900 (1). These reports were followed by small studies that suggested benefit with oxygen supplementation in acute MI, but these studies were limited by lack of randomization and unblinded end point ascertainment (2-4). Nonetheless, supplemental oxygen was incorporated into routine clinical practice, as evidenced in 2007 cardiology practice guidelines that recommended routine supplemental oxygen to all patients with acute coronary syndrome during the first 6 h after presentation (5). This widespread belief in oxygen was highlighted in a survey of emergency department, cardiology, and ambulance staff in which 98% of respondents reported using oxygen supplementation

for suspected MI and 55% believed oxygen reduced the risk of death (6).

Despite the ubiquitous use of oxygen, there were early reports of potential harm with high-dose oxygen supplementation in individuals with acute MI (7). Over 40 years ago, the first randomized trial of high-dose oxygen in patients with an acute MI demonstrated that oxygentreated patients had increased cardiac enzymes and a trend toward increased mortality compared with those not treated with oxygen (8). More recently, a study of 441 patients with ST-segment elevation MI, but without hypoxia, demonstrated that supplemental oxygen therapy (8 L/min) was associated with increased markers of myocardial injury, increased rate of early MI, and larger myocardial infarct size at 6 months compared with ambient air (9). In this setting, the DETO2X-AMI (Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction) trial was performed (10). The DETO2X-AMI trial was an openlabel, registry-based clinical trial that randomized 6,629 patients with suspected acute MI and oxygen saturation ≥90% to receive supplemental oxygen at 6 L/min for 6–12 h or ambient air (10). While supplemental oxygen prevented hypoxemia compared with the control group, supplemental oxygen did not improve the primary outcome of 1-year mortality (hazard ratio 0.97, 95% CI 0.79–1.21; P=0.80). A subsequent meta-analysis of randomized clinical trials, including the DETO2X-AMI trial, demonstrated that supplemental oxygen therapy did not reduce the risk of in-hospital (odds ratio 1.11, 95% CI 0.69–1.77) or 30-day mortality (odds ratio 1.09, 95% CI 0.80–1.50) in those with suspected acute MI without hypoxia (11).

In this issue of Diabetes Care, Nyström et al. (12) present results of a prespecified analysis of the DETO2X-AMI trial among individuals with diabetes and a confirmed MI, a particularly high-risk cohort. Of the 5,010 individuals with confirmed MI enrolled in the DETO2X-AMI trial, 19% had diabetes. In the group with diabetes, the incidence of the primary composite outcome (total mortality, rehospitalization for MI, or rehospitalization for heart failure) at 1 year and the incidences of individual components of the composite outcome were similar in those treated with supplemental oxygen compared with ambient air. There was no statistical interaction between treatment and diabetes status for any of the outcomes. However, although not observed in individuals without diabetes and not statistically significant, the short-term adverse outcomes were

Corresponding author: David Aguilar, david.aguilar@uth.tmc.edu

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<sup>&</sup>lt;sup>1</sup>Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, and Division of Cardiology, University of Texas McGovern Medical School, Houston, TX

<sup>&</sup>lt;sup>2</sup>Michael E. Debakey Veterans Affairs Medical Center, Houston, TX

<sup>&</sup>lt;sup>3</sup>Center for Cardiometabolic Disease Prevention, Department of Medicine, Baylor College of Medicine, Houston, TX

numerically greater in patients with diabetes receiving oxygen supplementation compared with those breathing ambient air. For example, in-hospital death occurred in 13 (2.9%) patients receiving oxygen compared with 7 (1.4%) who were randomized to ambient air. Similar numerical trends were seen for in-hospital cardiogenic shock, cardiac arrest, and 30-day allcause mortality, although conclusions are limited by very small numbers of events. As anticipated, individuals with diabetes had worse clinical outcomes following MI than those without diabetes, including increased risk of death at 1 year.

Previous randomized trials of oxygen supplementation in acute MI have been limited by small sample size and, thus, have been unable to identify particular subgroups that may receive benefit or harm. Although the current study provides new and needed information regarding oxygen supplementation for those with diabetes, it remains limited in power for this subgroup. As described in the main publication on the DETO2X-AMI trial (10), mortality was lower than anticipated, potentially related to the exclusion of hypoxemic patients, a higher-risk subset. Future and ongoing studies, such as an oxygen supplementation trial of 21,000 individuals with suspected acute coronary syndrome, should provide further subgroup information (13). Nonetheless, the current analysis from the DETO2X-AMI trial does not support the use of supplemental oxygen in individuals with diabetes and acute MI who have normal oxygen saturations. Furthermore, albeit limited by small number of early events (<30 days), the study does not exclude the possibility of harm from oxygen supplementation during the early period of an acute MI in those with diabetes.

How might oxygen be harmful in individuals with diabetes and acute MI? Several studies have shown detrimental effects of hyperoxia, including increased coronary vascular resistance, reduced coronary artery blood flow, and regional decrease in myocardial function (14–16). Hyperoxia may also increase production of oxygen free radicals and oxidative stress, which in turn may lead to cardiac injury (15,17). Importantly, endothelial dysfunction, microvascular abnormalities, increased oxidative stress, and

cardiac cellular metabolic dysregulation are all hallmarks of diabetic cardiovascular disease (18) that may be further exacerbated by hyperoxia. Hyperoxia has also been recognized to reduce heart rate, reduce cardiac output, and increase systemic vascular resistance (19). Of note, the majority of these studies have used high concentrations of oxygen, achieving arterial partial pressure of oxygen values ranging from 273 to 600 mmHg (14,19); the cardiac effects with more modest oxygen supplementation as may happen in clinical practice have not been well studied.

In 1775, the clergyman and chemist Joseph Priestly, one of the discoverers of oxygen, recognized the potential therapeutic use of oxygen ("dephlogisticated air") but warned of possible danger: "... for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, live out too fast and the animal power be too soon exhausted in this pure kind of air. A moralist, at least, may say that the air which nature has provided for us is as a good as we deserve" (20). Recent data are consistent with this observation that "natural" ambient air is sufficient in those presenting with acute MI and normal oxygen saturation, a recommendation reflected in recent treatment guidelines for acute MI (21).

**Duality of Interest.** V.N. was the site principal investigator of a study sponsored by Merck and holds a provisional patent along with Baylor College of Medicine and Roche on use of biomarkers in prediction of heart failure. No other potential conflicts of interest relevant to this article were reported.

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Aguilar and Nambi 2021

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