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EDITORIAL COMMENT

Oxygen for Myocardial Infarction

Not an Open Bar!*

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Following the discovery of oxygen by Schielle, Priestly, and Lavoisier in the late 18th century, the same authors described the toxicity of this gas (1). Despite numerous studies that subsequently confirmed the risks, there was no limitation on the liberal use of oxygen until recently. The veneration of this gas originally called "elixir of life" or "vital gas" has long seemed stronger than the mass of data demonstrating its deleterious effects. The mechanisms of systemic toxicity are mainly related to the increase in production and the accumulation of reactive oxygen species (ROS) that cause cell damage, and vasoconstriction via the reduction of endothelial NO; however, other mechanisms have also been described (2). In particular, the effects of hyperoxia on the coronary arteries have been known for more than 70 years, but the clinical impact of this toxicity has remained limited. Yet the wind seems to have changed in the past decade, with several publications providing compelling data against the liberal use of oxygen, including several randomized trials that show an increase in morbimortality in hyperoxemic intensive care patients (3), with a striking dose effect (4), and with ineffectiveness of moderate doses of oxygen in the acute phase of myocardial infarction (5) and deleterious effects at higher doses (6,7).

During the first half of the 20th century, several authors argued for the use of oxygen during myocardial infarction and associated chest pain (8,9). The rationale for oxygen use to decrease chest pain associated with myocardial infarction is, as many medical students have learned until recently, to increase the tissue "oxygenation" of the ischemic myocardium. Consequently, the reduction of ischemia would decrease mediator production that trigger cardiac chemosensitive nociceptors. Paradoxically, instead of decreasing the ischemia, hyperoxemia may promote tissue ischemia. As early as 1947, with the improvement of techniques that measure coronary blood flow, Eckenhoff et al. (10) showed that the administration of 100% oxygen reduced the coronary blood flow within a few minutes. Subsequently, work from Russek et al. (11) in 1950 demonstrated that oxygen in nonhypoxic patients is ineffective or may be deleterious when used for this indication. Russek et al. (11) showed that the administration of 100% oxygen aggravated the electrocardiographic signs of myocardial ischemia and did not decrease chest pain, unlike nitroglycerin administration. The authors concluded that the administration of high oxygen flow was not trivial and that "its indiscriminate employment may cause more harm than good," which could still be written identically today. Physiological studies have consistently shown that hyperoxia lowers coronary blood flow, increases coronary resistance, and decreases cardiac output (12).

Several randomized controlled trials have subsequently demonstrated either increased coronary risks when using high oxygen flows (6,7) or pointlessness at moderate flow rates during the acute phase of myocardial infarction (5). However, very few studies have specifically evaluated the impact of oxygen on chest pain that accompanies myocardial infarction.

SEE PAGE 1590

In this issue of *JACC: Cardiovascular Interventions,* the study by Sparv et al. (13) is a substudy of the DETO2X-AMI (The Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction) randomized controlled trial, and was conducted in 8 Swedish hospitals (the whole study was conducted in 35 centers), it evaluated the effect of moderate-dose

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oxygen supplementation on chest pain (5). The main study compared the routine use of moderate oxygen flow rates (6 l/min) and air (with oxygen administration restricted to when oxygen saturation was <90%) during acute myocardial infarction. There was no difference in mortality between the 2 groups (5). The substudy by Sparv et al. (13) is a robust demonstration of the uselessness of oxygen to decrease thoracic pain during acute myocardial infarction in nonhypoxemic patients. A few limitations of the study should be discussed. In the Sparv et al. (13) study, only 9.4% (624 of 6,629) of patients in the main study were evaluated for the impact of oxygen on pain. Participating centers were recruited based on the assessment of thoracic pain in the acute phase of myocardial infarction using a visual analog scale (VAS). The primary endpoint of the study was used to calculate the sample size with a hypothesis of a 15% difference on the VAS pain scale, but the sample size was not calculated to demonstrate equivalence. Moreover, the main judgment criterion of the study is based on a fairly basic and subjective evaluation, the VAS, this limit being recognized by the authors in the discussion. Last, the potential harm caused by higher oxygen flow rate, which was found in previous studies (6,7), as well as prolonged oxygen exposure in this population was not evaluated in this study.

No difference in peak chest pain or use of painkillers or sedatives was found. These results are in line with 2 other recent studies published by the same team (14,15). Sparv et al. (13) conclude that there is no favorable effect of moderate-dose oxygen to reduce chest pain during infarction and encourage, in line with the most recent recommendations, the use of oxygen only in patients with an SpO_2 <90% (16,17).

Oxygen therapy has been used liberally in myocardial infarction for more than a century, and it is time to use it properly, that is: 1) to treat hypoxemia if it is present; and 2) to avoid hyperoxemia. It is worth mentioning that in the DETO2X-AMI and AVOID (Air Versus Oxygen in Myocardial Infarction) studies, <10% of patients received oxygen for hypoxemia in the control groups (no systematic oxygen supplementation) (5,7).

It is often difficult to understand the obstacles in the application of clinical recommendations; however, in the case of oxygen therapy, there are in fact some specific obstacles. The lack of continuous monitoring of oxygenation has long been a hindrance to oxygen adjustment; second, the focus has been mainly on the development of new drugs at the end of the last century. It is only in the last 10 years that the clinical impact of oxygen in different situations and in particular in coronary ischemia has been under the spotlight. Oxygen should not be used to relieve thoracic pain as well as it should not be used to relieve dyspnea as it was recently underlined by the British Thoracic Society guidelines (18). Oxygen should be used and thought of as a drug with a specific indication and a therapeutic range, and consequently administered only to treat hypoxemia with careful titration of therapy to avoid hyperoxemia.

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