

VIEWPOINT

## Revisiting the Role of Oxygen Therapy in Cardiac Patients

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Over the past century, multiple studies lacking the precision of today's advanced technology provided conflicting data on the effects of oxygen therapy in normoxic cardiac patients. More importantly, no randomized, blinded, controlled studies have shown a benefit of such treatment. Yet the use of supplemental oxygen is widespread in cardiac patients. In these conditions, inadvertent hyperoxia commonly occurs because of concerns to ensure sufficient oxygenation and because hyperoxia is not perceived to be detrimental. In recent years, there has been mounting evidence demonstrating the potential adverse effects of hyperoxia on the cardiovascular system. In this report, we review data examining the effects of supplemental oxygen in normoxic patients with acute presentations of coronary artery disease. It is also the aim of this report to emphasize the point that oxygen therapy might have major adverse physiologic effects that must be considered when it is employed. (J Am Coll Cardiol 2010;56:1013-6) © 2010 by the American College of Cardiology Foundation

Between 1940 and 1970, the cardiovascular effects of hyperoxia were extensively investigated. These studies suggested that hyperoxia reduced coronary blood flow (CBF) (1), heart rate, cardiac output/index (1-3), and cardiac oxygen consumption (4), while evoking a rise in blood pressure, systemic vascular resistance, and the augmentation index, a measure of large artery stiffness (3).

### The Rationale for Oxygen Therapy in Acute Coronary Syndromes

The American College of Cardiology/American Heart Association task force (ACC/AHA 2007 guidelines) has assigned Class I recommendation for oxygen use to correct arterial oxygen desaturation ( $\text{SaO}_2 < 90\%$ ) and Class IIa recommendation for *all* patients with unstable angina/non-ST-segment elevation myocardial infarction and uncomplicated ST-segment elevation myocardial infarction within the first 6 h after presentation. The rationale for oxygen use is based on 2 assumptions: 1) that increasing arterial oxygen tension decreases the acute ischemic injury and the eventual infarct area (5,6); and 2) the observation that some patients with uncomplicated myocardial infarction have arterial hypoxemia due to fluid retention in the lungs and a ventilation-perfusion mismatch.

However, the evidence supporting these assumptions is limited. Moreover, we are not aware of any studies demonstrating that normoxic subjects undergoing percutaneous coronary intervention for acute myocardial infarction derive any benefit from supplemental oxygen. Furthermore, there is no evidence supporting the common practice of oxygen therapy after successful percutaneous coronary intervention.

Two studies from the 1970s (5,6) were crucial to the development of the current oxygen therapy guidelines in acute coronary syndromes (ACS).

Maroko et al. (5) demonstrated in dogs that 40% oxygen reduced electrocardiographic, histological, and biochemical evidence of myocardial ischemic injury. Unfortunately, the sequence of gas mixture delivery during ventilation was not randomized and the ST-segment elevation measurements were not blinded. Madias and Hood (6) examined the effects of supplemental oxygen (delivered via a face mask) in patients with anterior myocardial infarction. Using precordial ST-segment mapping, these authors noted a 16% reduction in both the sum of ST-segment elevations and the number of recording sites demonstrating ST-segment elevation. However, the study was not randomized, ST-segment measurements were not blinded, and the timing of precordial mapping was not standardized. Moreover, the duration of oxygen inhalation varied greatly among subjects (48 to 80 min).

Rawles and Kenmure (7) performed the first randomized, double-blinded, controlled trial of oxygen therapy in the setting of uncomplicated myocardial infarction. After excluding 43 patients from the initial 200 subjects, 77 and 80 patients were enrolled in the air and oxygen groups, respectively. Either oxygen or compressed air at a flow rate of

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**Abbreviations and Acronyms**

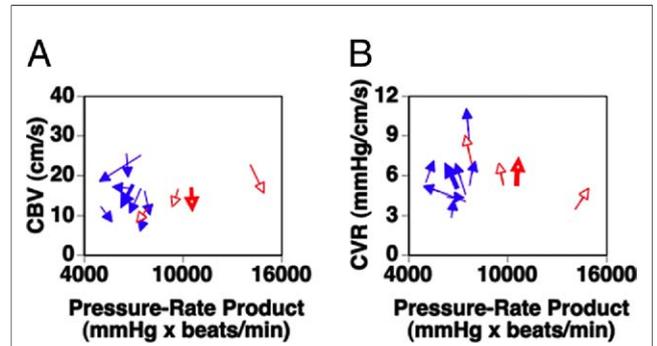
- ACS** = acute coronary syndromes
- CBF** = coronary blood flow
- CBV** = coronary blood velocity
- CVR** = coronary vascular resistance

6 l/min was administered by mask throughout the first 24 h. Only diamorphine was employed as medication. All parameters were comparable except higher PaO<sub>2</sub> and aspartate aminotransferase levels were noted in the oxygen group. This study showed no benefit of oxygen therapy in reducing arrhythmias or mortality. On the contrary, supplemental

oxygen elevated aspartate aminotransferase levels, suggesting infarct expansion. Of note, the mortality rate in the oxygen group was 11.3% compared with 3.9% in the control group, although this difference was not statistically significant.

**Coronary Vasoconstriction During Hyperoxia**

Recently, duplex ultrasound (HDI 5000, ATL Ultrasound, Bothell, Washington) has been employed to measure coronary blood velocity (CBV) (a CBF surrogate) in the left anterior descending coronary artery of 7 healthy subjects (8). CBV and coronary vascular resistance (CVR) were measured while breathing room air and after exposure to hyperoxia (100% O<sub>2</sub>) for 5 min. Hyperoxia decreased CBV by 15 ± 3% (p < 0.01) and raised CVR by 20 ± 4% (p < 0.01). Similar findings were observed in 3 cardiac transplant patients who underwent transplantation 5 to 14 months earlier (CBV decreased by 16 ± 2% [p < 0.01], and CVR increased by 23 ± 3% [p < 0.01]) (Figs. 1 and 2), indicating a direct vasoconstrictor effect of hyperoxia on the coronary circulation not mediated through autonomic reflexes. These noninvasive observations are consistent with the work of McNulty et al. (9) who examined the effects of hyperoxia on the coronary circulation using intracoronary Doppler flow wire and coronary angiography in stable patients with coronary arterial disease (coronary stenosis <50% and



**Figure 2** Individual and Mean Responses of CBV and CVR in Normal Subjects and Transplant Patient

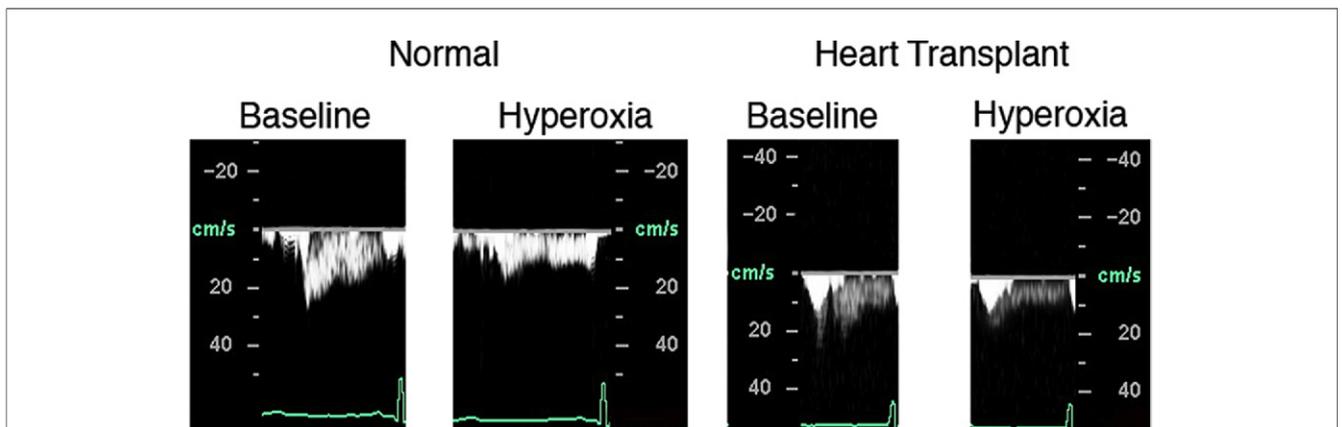
Solid blue arrows indicate normal subjects, and open red arrows indicate transplant patient. Solid blue and red arrows represent mean values for normal subjects and the 3 heart transplant patients, respectively. The pressure-rate product is an index of myocardial O<sub>2</sub> consumption. CBV = coronary blood velocity; CVR = coronary vascular resistance.

ejection fraction >50%). Hyperoxia decreased CBF by 29% and raised CVR by 41% (Fig. 3).

**Potential Mechanisms of Hyperoxic Coronary Vasoconstriction**

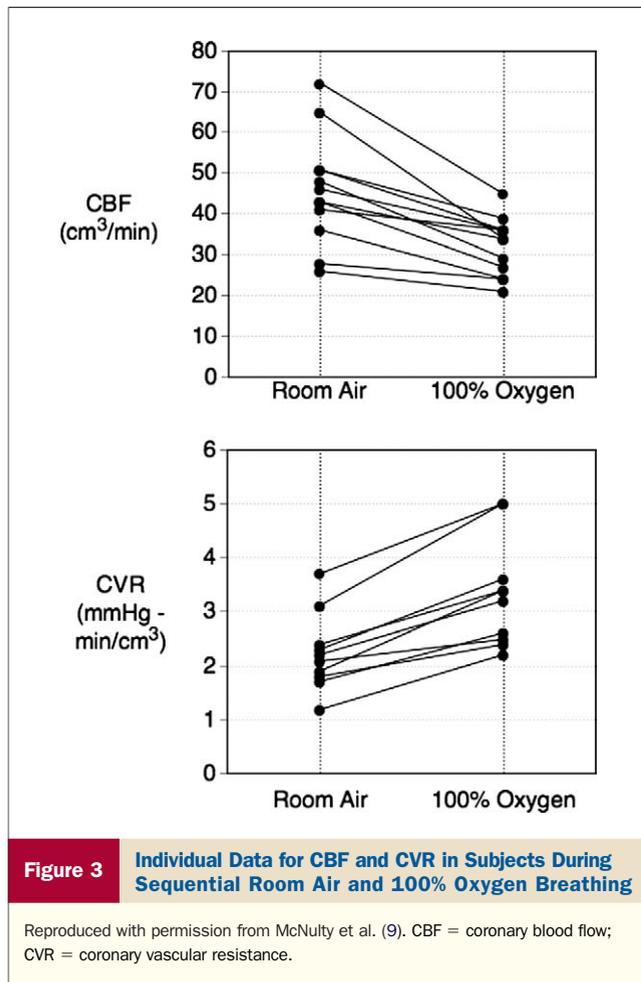
**Hyperoxia leads to the generation of reactive oxygen species.** Mounting evidence supports the hypothesis that hyperoxia leads to the generation of reactive oxygen species, which in turn decreases the bioavailability of nitric oxide and results in vasoconstriction (10). McNulty et al. (11) demonstrated that an intravenous infusion of vitamin C (a potent antioxidant) quickly restores and prevents coronary vasoconstriction during hyperoxia.

**The role of K<sup>+</sup><sub>ATP</sub> channels in hyperoxia-induced vasoconstriction.** During hypoxia and ischemia, a fall in the intracellular ATP concentrations mediates the opening of ATP-sensitive potassium channels, which in turn causes



**Figure 1** Pulsed Doppler Recording of Left Anterior Descending Coronary Artery in Healthy Subjects and Cardiac Transplant Patients

Blood flow velocity is significantly decreased in both groups during hyperoxia.



hyperpolarization of the vascular smooth muscle cells and vasodilation. Animal studies have shown that  $K^+_{ATP}$  channels play an important role in regulating coronary artery blood flow at rest and during hypoxia and ischemia (12). Mouren et al. (13) demonstrated that hyperoxic coronary vasoconstriction is mediated through the closure of  $K^+_{ATP}$  channels.

**Hyperoxia can induce vasoconstriction by acting directly on L-type  $Ca^{2+}$  channels.** Animal studies (14) demonstrate that oxygen-sensitive L-type calcium channels are present on vascular smooth muscle cells. They contribute to the local circulatory control during hypoxia and hyperoxia. **Hyperoxia may affect the release of angiotensin II with subsequent changes in endothelin-1 levels.** Isolated cardiac myocyte studies demonstrate that angiotensin I is produced with hyperoxia and is subsequently converted to angiotensin II, possibly on the surface of endothelial cells. Angiotensin II promotes endothelin-1 release and thereby increases vascular tone (15).

**Hyperoxia increases the production of potent vasoconstrictor 20-HETE.** Hyperoxia induces the production of 20-HETE, an arachidonic acid metabolite. 20-HETE is a constrictor and plays an important role in myogenic regulation (16).

## Myocardial Oxygen Consumption During Hyperoxia

One could speculate that an increase in oxygen extraction in ACS would compensate for the decreased CBF seen with oxygen. Animal studies suggest that a high  $PO_2$  decreases myocardial oxygen consumption independent of heart rate, cardiac performance and metabolic requirements. High  $PO_2$  decreases capillary density, which in turn may limit oxygen diffusion and extraction (17,18). Reinhart et al. (19) confirmed that in critically ill patients, high-flow oxygen therapy causes a misdistribution of microcirculatory blood flow with increased functional  $O_2$  shunting and a reduction in total-body oxygen consumption (total-body oxygen uptake decreased by 10% due to an 18% decrease in  $O_2$  extraction). Thus, high-flow oxygen, despite improving oxygenation, may not improve organ-specific oxygen delivery.

## Summary

We believe that supplemental oxygen is used excessively, especially in cardiac patients to maintain oxyhemoglobin saturations close to 100%; unknowingly, many of these patients are exposed to significant periods of hyperoxia. This occurs for 3 main reasons: 1) many medical staff (including physicians) do not recognize that oxygen is a vasoactive substance; 2) when transcutaneous blood oxyhemoglobin saturation approaches 100%, further increases in blood oxygen tension are not detected; and 3) oxygen tension is not adequately monitored, especially in the setting of high-flow oxygen therapy.

Although the use of oxygen is clearly appropriate and advisable to treat hypoxia, we hypothesize that excessive use of supplemental oxygen in normoxic cardiac patients could potentially lead to worse outcomes in a number of patients. The current guidelines of oxygen therapy are not based on randomized, double-blinded, controlled studies. We propose that such studies are imperative to delineate the precise role of oxygen therapy in these conditions. In the interim, the potential physiologic ramifications of such therapy should be considered.

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**Key Words:** CAD ■ hyperoxia ■ oxygen.