

## The mechanisms of coronary artery vasoconstriction upon hyperoxia: a mini-review



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### ABSTRACT

Oxygen supplementation is potentially harmful in patients with acute coronary syndrome as it may lead to hyperoxia-induced coronary vasoconstriction. This phenomenon may deteriorate the already poor coronary perfusion. The exact physiology mechanisms of how hyperoxia causes vasoconstriction are still not fully elucidated. Some hypotheses were proposed, among others: 1) reduced nitric oxide (NO) bioavailability due to increased reactive oxygen species (ROS) generation; 2) hyperoxia-induced ATP-sensitive potassium channel closure; 3) activation of smooth muscles' oxygen-sensitive calcium channel; 4) increased endothelin-1 release; and 5) increased production of 20-hydroxyeicosatetraenoic acid (20-HETE). A decent understanding of this phenomenon will aid in more awareness and better clinical management.

**Keywords:** hyperoxia, coronary artery, vasoconstriction, mechanisms

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### INTRODUCTION

Oxygen supplementation with a fraction of inspired oxygen (FiO<sub>2</sub>) of >21% may trigger hyperoxemia (PaO<sub>2</sub> >100 mmHg) and eventually cause hyperoxia, which is elevated oxygen concentration within the tissue.<sup>1</sup> Hyperoxia will exert an adverse effect on acute coronary syndrome.<sup>2-4</sup> Hyperoxia may reduce cardiac output,<sup>5</sup> coronary blood flow,<sup>6,7</sup> left ventricle (LV) perfusion,<sup>8</sup> systemic and coronary oxygen delivery,<sup>9</sup> and increase vascular resistance.<sup>1</sup> In addition to that, hyperoxia may also trigger the formation of reactive oxygen species (ROS) which contribute to coronary artery vasoconstriction.<sup>10</sup> Furthermore, ROS may also induce leucocyte chemotaxis, inflammation process, and oxidative stress.<sup>11</sup> Increased oxidative stress will compromise heart electrophysiology and consequently will increase the risk of arrhythmia.<sup>12</sup> In clinical practice, vasoconstriction which is caused by hyperoxia, might result in underestimation of blood vessel size during angiography. If the procedure is followed by percutaneous coronary intervention (PCI), it might risk stent thrombosis.<sup>13</sup> European Society of Cardiology (ESC) Guidelines in acute coronary syndrome recommend oxygen supplementation only

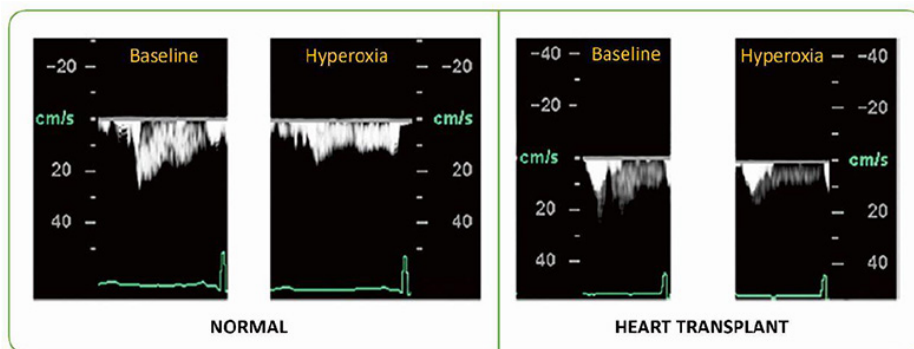
for patients with hypoxia (arterial oxygen saturation less than 90%), or those with signs of respiratory distress.<sup>14,15</sup>

The exact physiology mechanism of how hyperoxia causes vasoconstriction of coronary arteries in humans cannot yet be clearly explained. Some hypotheses based on animal and in vitro studies have been proposed. This mini-review would like to discuss the mechanisms behind coronary artery vasoconstriction in humans.

### Coronary vasoconstriction during hyperoxia

Momen et al., have demonstrated hyperoxia effect on blood flow rate and

left anterior descending (LAD) coronary artery vascular resistance utilizing duplex ultrasonography non-invasively on healthy individuals and post-heart transplant patients.<sup>16</sup> As a baseline, blood flow rate and coronary vascular resistance are measured. At the same time, the subjects breathe room air, and then the same measurement is performed again after the supplementation of 100% oxygen for 5 minutes. Lowered blood flow rate and increased vascular resistance as opposed to baseline were observed significantly in the healthy individuals as well as in post-heart transplant patients (each with p<0.01) (Figure 1).<sup>16</sup>

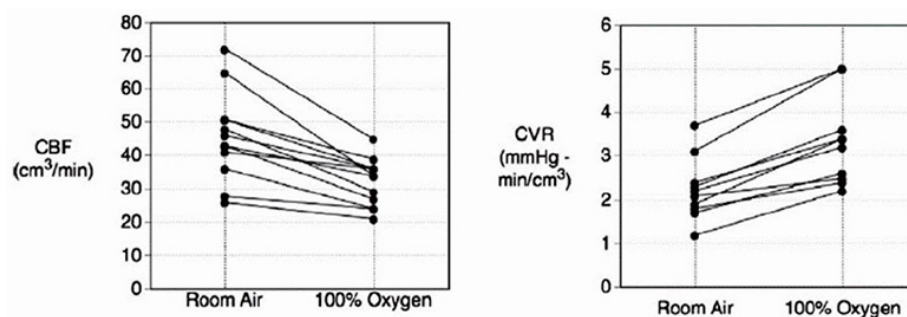


**Figure 1.** Pulsed wave doppler record on LAD: significantly lower blood flow rate was observed on healthy individuals as well as on post-heart transplant patients<sup>16</sup>

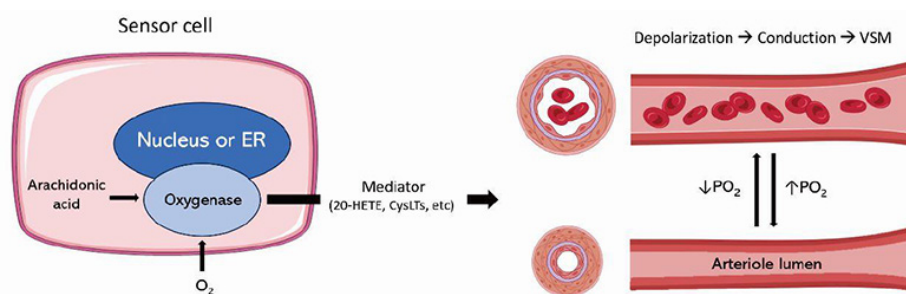
A study on the effect of hyperoxia on the coronary artery has also been performed with the invasive method by McNulty et al., utilizing Intravascular Ultrasound (IVUS) and angiography on chronic coronary syndrome patients (coronary stenosis of <50% and LV ejection fraction of >50%). The study has observed a 29% reduction in coronary blood flow and a 41% rise in vascular resistance (Figure 2).<sup>7</sup>

### Mechanism of vasoconstriction in hyperoxia

Several hypothetical mechanisms are considered to explain coronary vasoconstriction in hyperoxia, among others potentially: 1) Lowered NO bioavailability caused by ROS. Hyperoxia has promoted the formation of ROS through various enzymatic pathways.<sup>17</sup> One is through NO synthase (NOS) catalyzed, an enzyme that also produces NO. Increased ROS will restrict NO formation.<sup>11</sup> NO is a molecule that can relax the smooth muscle of the blood vessel. Lowered NO concentration will contribute to vasoconstriction.<sup>10</sup> 2) Closure of ATP-sensitive potassium channels ( $K^+_{ATP}$ ). An animal study has demonstrated the important role of  $K^+_{ATP}$  channels in coronary artery blood flow regulation. In ischemia and hypoxia conditions, intracellular ATP concentration is reduced, resulting in the opening of  $K^+_{ATP}$  channels, which then trigger hyperpolarization of vascular smooth muscle and subsequent vasodilation.<sup>18</sup> In hyperoxia conditions, vasoconstriction is mediated by the closure of  $K^+_{ATP}$  channels.<sup>19</sup> 3) Activation of Type L Calcium ( $Ca^{2+}$ ) channels. Animal studies discovered type L  $Ca^{2+}$  channels, which are oxygen-sensitive in smooth muscle cells. These channels contribute to local circulation regulation; thus, increased oxygen pressure might induce smooth muscle contraction.<sup>20</sup> 4) Release of Endothelin-1. In an experimental setting, cardiomyocyte isolate produces angiotensin I when oxygen pressure is increased. Angiotensin I readily convert into Angiotensin II on the surface of blood vessels. Angiotensin II stimulates the endothelial cells to release endothelin-1, which then causes increased vascular tone. When oxygen pressure is lowered, cardiomyocytes produce adenosine that will block the



**Figure 2.** Reduced CBF and increased CVR in hyperoxia state were observed on IVUS measurement. CBF (coronary blood flow); CVR (coronary vascular resistance); IVUS (intravascular ultrasound)<sup>7</sup>



**Figure 3.** Hyperoxia triggers the formation of 20-HETE, a strong vasoconstrictor<sup>22</sup>

$\alpha$ -adrenergic agonist effect and lower the vascular tone.<sup>21</sup> 5) Increased production of 20-HETE. 20-hydroxyeicosatetraenoic acid (20-HETE) is the metabolic product of arachidonic acid by the cytochrome family. The formation of 20-HETE is induced by increased oxygen pressure and is triggered by oxidative stress (Figure 3).<sup>22</sup> 20-HETE is a strong vasoconstrictor. 20-HETE generally restrict the formation of vascular NO, except in lung vascular, whereas 20-HETE increase the formation of NO.<sup>23-26</sup>

### CONCLUSION

Coronary artery vasoconstriction is one of the adverse effects of hyperoxia in acute coronary syndrome. Several hypotheses have been proposed in order to explain the mechanism of how hyperoxia can cause coronary artery vasoconstriction, which is lowered NO bioavailability caused by ROS, closure of  $K^+_{ATP}$  channels, activation of type L  $Ca^{2+}$  channels, endothelin-1 release, and formation of 20-HETE. There must be other mechanisms outside of those discussed in this article. Hopefully, this article will provide insight into the

vasoconstriction phenomenon related to hyperoxia and will inspire further study on this subject.

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### AUTHORS' CONTRIBUTION

MII conceived the idea, performed the literature search, and mainly designed the review. MII contributed to writing the manuscript. IPD has edited the manuscript for publication. YHO reviewed the article before submission. All authors read and approved the final manuscript.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

### ETHICAL APPROVAL

Not applicable.

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