

## Chapter 6

# Cardiac Remodeling Under Hyperoxic Conditions: Hyperoxia and Heart Diseases

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### ABSTRACT

*Cardiovascular complications and arrhythmias account for high mortality in cardiopulmonary patients in intensive care units (ICU) and critical care units. Patients in ICU are often administered with 100% oxygen for treatment with many diseases. According to American Heart Association (AHA), more than 2200 deaths related to cardiac failure are reported every day with an average of 1 in every 39 seconds. Cardiomyopathy is also reported in many diseased conditions including acute lung injury, diabetes, obesity, hypertension, and cancer. Recent studies indicate that hyperoxia induces cardiac injury due to dysfunctional lung and compromised pulmonary functioning. The exact mechanism of cardiovascular complications in ICU/ critical care remains unknown. This review will discuss the effect of hyperoxia on cardiac remodeling with more emphasis on ventricular and electrical remodeling. Understanding the exact mechanism of hyperoxia induced cardiomyopathy is not only important to understand the disease development and progression but also open new avenues for targeted therapy.*

### INTRODUCTION

Administration of 100% oxygen (O<sub>2</sub>) is widely used intervention in critically ill patients at Critical care or Intensive Care Units (ICU). Although O<sub>2</sub> administration is supported by many guidelines for the patients with various medical emergencies (Anderson et al., 2007; Dickstein et al., 2008; O'Driscoll et al., 2008), the clinical implication of hyperoxia remain an important subject of debate (Altemeier & Sinclair, 2007). Recent studies indicate that hyperoxia induces cardiac injury due to dysfunctional lung and compromised pulmonary functioning (Visser, Walther, Laghmani el, Laarse, & Wagenaar, 2010). As pulmonary and cardiovascular systems are known to be in cooperative regulation, changes in cardiovascular systems may influence pulmonary function and vice versa (Howden et al., 2012b). Further-

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more, smoke inhalation induced lung injury has been shown to have cardiovascular changes in previous study (Demling, Lalonde, Youn, & Picard, 1995) and continuous exposure of rabbits to hyperoxia for 72h caused elevated heart rate and low blood pressure (Sventek & Zambraski, 1988) indicating a close regulation between cardiovascular and pulmonary systems. More recent studies exploring the functional implications of hyperoxia from a cardiovascular stand point identify functional changes in heart rate and heart rate variability and linked it to polymorphisms and candidate gene loci (Howden et al., 2012b). Although the damage caused by delivering 100% oxygen treatment is to the lung and pulmonary system, patients supplemented with 96% of oxygen (hyperoxic), causes accumulation of lung fluid leading to pulmonary dysfunction causing oxidative stress in the heart. Additionally, many clinical reports indicating that hyperoxia was independently associated with increased in-hospital mortality in ICU following resuscitation from cardiac arrest, stroke, and traumatic brain injury (Damiani et al., 2014; Helmerhorst et al., 2014; Kilgannon et al., 2010; Nelskyla, Parr, & Skrifvars, 2013; Rincon, Kang, Maltenfort, et al., 2014; Rincon, Kang, Vibbert, et al., 2014).

## **Hyperoxia and Lung Injury**

Administration of supraphysiological concentrations of oxygen as a mechanical ventilation is often a standard practice to treat newborns, older children, and adults with various diseases and surgeries (Andrea Porzionato et al., 2015). Nevertheless, there were also concerns that breathing pure O<sub>2</sub> might cause irreparable harm and death, which became a prominent clinical concern with the emergence of ICU in 1960s (Kallet & Matthay, 2013). Hyperoxia can cause lung cell injury and death due to accumulation of extremely toxic reactive oxygen species (ROS) (Xu, Guthrie, Mabry, Sack, & Truog, 2006). Induction of extensive inflammatory response and damage to the alveolar-capillarity barrier, which can lead to impaired gas exchange and pulmonary edema are the characteristics of hyperoxia induced lung injury. These characteristics are known to be accompanied by injury and apoptotic or necrotic death of pulmonary cells (Mantell & Lee, 2000; Petrache et al., 1999). Hyperoxia can also induce acute and chronic lung diseases such as acute inflammatory lung injury and bronchopulmonary dysplasia (BPD) under prolonged exposure (Andrea Porzionato et al., 2015).

Generation of ROS including superoxide anions, hydrogen peroxide, hydroxyl radicals, and hypochlorous acid by activated NADPH oxidase, which in turn injure pulmonary cells via lipid peroxidation, protein sulfhydryl oxidation, enzyme inactivation, DNA damage, and depletion of cellular reducing agents (Figure 1) are some of the events that occur in acute inflammatory lung injury (Cacciuttolo, Trinh, Lumpkin, & Rao, 1993; X. Zhang et al., 2003). This can also induce endothelial and epithelial cells to stress responses, and modulation of cell growth, inflammation, and/or death (Lee & Choi, 2003).

The most common chronic lung disease of prematurity is BPD, which results in impaired alveolar growth and a dysmorphic vascular architecture (Thébaud & Abman, 2007). Hyperoxia or high oxygen concentrations are directly correlated to BPD and most of the animal models of BPD involve hyperoxic exposure. Disruption of postnatal alveolar development leading to smaller numbers of enlarged and simplified alveoli, thick septa, and an increase in alveolar macrophages are some of the pathophysiological effects for BPD (Balasubramaniam, Mervis, Maxey, Markham, & Abman, 2007; Dager et al., 2003; Grisafi et al., 2013; Grisafi et al., 2012; A. Porzionato et al., 2012; A. Porzionato et al., 2013). Changes in microvascular development and thickening of the medial muscle layer of arteries, pulmonary hypertension, increase in number of lung mast cells, which eventually accumulate around the vessels are also reported in experimental models of BPD (Brock & Giulio, 2006; Grisafi et al., 2013; Grisafi et

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