Obesity and lung disease: a toxic mix.

Obesity is a major worldwide health problem that causes significant disability and reduces life expectancy through its adverse affects on the major organ systems of the body including the lungs. In this issue of the Journal, Yilmaz et al provide valuable new insights into the mechanisms through which obesity exerts its damaging actions on the lung (Yilmaz, 2015).

Obesity is associated with an increased incidence of lung diseases including such common conditions as asthma, COPD, ARDS, sleep apnoea syndrome and pulmonary hypertension (Piper and Grunstein, 2011, Sood, 2010, Han et al., 2007). The adverse effects of obesity on the respiratory system are mediated by a number of mechanisms including the production of pro-inflammatory cytokines by adipose tissue, mechanical restriction of thoracic volumes and obesity-induced hypoventilation (Han et al., 2007, Piper and Grunstein, 2011, Sood, 2010).

The non-diseased lung is exposed to chronic hypoxia following ascent to high altitude or when an individual develops a disorder of ventilation. One such disorder is the obesity hypoventilation syndrome ("Pickwickian syndrome"), a well recognized complication of obesity (Han et al., 2007, Piper and Grunstein, 2011). In these conditions the lung shows characteristic responses to sustained hypoxia including hypoxic pulmonary vasoconstriction, an initial acute inflammatory response and subsequently the development of sustained pulmonary hypertension with associated right ventricular hypertrophy. This hypertension is an adverse response and can, in

a minority of susceptible individuals, lead to right ventricular failure and death in the absence of any pre-existing pulmonary problems (Anand et al., 1990). In the presence of lung diseases, hypoxia pulmonary hypertension is an independent predictor of increased mortality.

While the development of pulmonary hypertension is an adverse, maladptive response of the lung to hypoxia, a second important response of the normal lung to hypoxia is angiogenesis and growth of the alveolar capillary membrane with an associated expansion of the pulmonary capillary bed (Cahill et al., 2012, Howell et al., 2009, Howell et al., 2003). The increased membrane diffusing capacity in humans who have acclimatized to high altitude suggests that similar hypoxia-induced alveolar capillary angiogenesis occurs in the human lung (Cerny et al., 1973, Martinot et al., 2013). This is a potentially beneficial adaptation to alveolar hypoxia as the expansion of the gas exchange membrane would facilitate oxygen uptake in the lung at a time when the partial pressure gradient driving oxygen into the capillary blood is reduced.

Since lungs diseases are commonly complicated by hypoxia, Yilmaz and colleagues asked the interesting question does obesity impair the normal adaptive changes in alveolar capillary structure seen in response to hypoxia? They found that in obese rats, the hypoxia induced increase in lung volume was attenuated compared to that in normal body weight animals, and that this attenuation was associated with reduced pulmonary compliance. Furthermore, they demonstrated that the reduction in compliance was observed even when measured in the open chest and in the isolated lungs showing that it was the result of a direct action of obesity on the lung

and not simply the result of mechanical restriction of chest wall movement. Such a restrictive defect represents a significant physiological disadvantage that might be further exacerbated in hypoxic lung diseases.

Despite the reduced compliance, the hypoxia-induced increases in the total surface area of the alveolar epithelial and capillary endothelial membranes were unaffected by obesity (Yilmaz, 2015). While this observation at first sight suggests a beneficial increase in the functional membrane diffusing capacity facilitating oxygen uptake, the measured carbon monoxide diffusing capacity was unaltered in both obese and lean animals. This was in large part because the increase in membrane surface area was counterbalanced by an increase in the (harmonic) mean diffusing distance from the alveolar gas to the erythrocytes. Some of this increase was the result of an hypoxia-induced increase in the interstitial cells and matrix within the alveolar walls. It may also have been caused by increase in the plasma layer between the endothelium and the erythrocytes.

Importantly hypoxia increased the thickness of the gas exchange membrane significantly more in the obese rats. If this effect were also seen in hypoxia induced by lung disease it would be a further potentially adverse effect of obesity in the lung that might worsen the underlying pulmonary disease.

Caution must be exercised when considering the implications of these findings. For example, all the physiological measurements, including the determination of membrane diffusing capacity, were made in the resting, profoundly anaesthetized animal. In this condition cardiac output is reduced and the reflex responses to

hypoxia markedly diminished. Furthermore, the volume of blood within the pulmonary capillaries is reduced from the normal awake, freely moving, state. Such reduction would have reduced the carbon monoxide diffusing capacity and may have altered the diffusing distance from the alveolar space to the erythrocytes. The situation in the awake, freely moving, exercising animal at much higher cardiac output is very different. The volume of capillary blood in the lung and the extent of perfusion of the pulmonary vascular bed increases at the higher cardiac outputs that occur in exercise. These changes in volume and flow are likely to alter the plasma component of the gas exchange membrane, potentially reducing its thickness. Higher cardiac output could also lead to more extensive perfusion of the expanded surface area of the gas exchange membrane, reducing the diffusion limitation of oxygen uptake observed in the hypoxic lung. Thus while Yilmaz and colleagues (Yilmaz, 2015) have identified important interactions between pulmonary hypoxia and obesity in the lung, further work is required to fully understand the consequences of these for gas exchange and disease outcomes when the two conditions coexist.

Previously, the adverse effects of obesity on the respiratory system have been attributed to a number of indirect effects including the production of pro-inflammatory cytokines by adipose tissue, mechanical restriction of thoracic volumes and obesity-induced hypoventaltion (Han et al., 2007, Piper and Grunstein, 2011, Sood, 2010). Yilmaz et al have shown for the first time that obesity alters important structural responses of the lung to hypoxia, identifying new avenues to be explored in understanding the adverse effects of obesity in lung diseases. Since hypoxia commonly complicates common pulmonary diseases, the role of these altered

responses in leading to the pulmonary complications of obesity warrants further investigation.

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