Anatomy & Physiology: Current Research
ISSN: 2161-0940

Bradford and O'Halloran, Anatom Physiol 2013, 3:1
DOI: 10.4172/2161-0940.1000e123

Editorial Open Access

Obstructive Sleep Apnoea, Intermittent Hypoxia and Respiratory Muscle Structure and Function

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Obstructive sleep apnoea is a common condition associated with significant morbidity and increased mortality. During sleep, the sub atmospheric pressure developed in the extra thoracic airway by the contraction of the thoracic pump muscles during inspiration causes collapse of the compliant upper airway, resulting in an episode of apnoea. Normally, upper airway collapse is prevented by contraction of upper airway muscles and if the airway does collapse, it is re-opened by a reflex augmented neural drive and greater contraction of these muscles. Therefore, the function of these muscles plays a critical role in the pathogenesis of the obstructive sleep apnoea. The multiple episodes of apnoea that occur during the course of sleep cause intermittent hypoxia. We have proposed that chronic intermittent hypoxia causes adverse changes in structure and function of upper airway muscle that result in an exacerbation of the condition. We have shown that chronic intermittent hypoxia in rats causes greater fatigability of upper airway, diaphragm and limb muscles. In general, this appears to be true also for chronic continuous hypoxia, although the diaphragm muscle is relatively tolerant of sustained hypoxia compared to limb muscle. We propose that the chronic intermittent hypoxia of obstructive sleep apnoea causes a positive feedback that exacerbates the condition by reducing upper airway muscle endurance, thus making the upper airway more vulnerable to collapse. This effect involves the generation of reactive oxygen species and treatment with antioxidants either prevents or ameliorates the adverse effects on muscle function, suggesting that antioxidants could be used as an adjunct therapy for obstructive sleep apnoea. This may be true also for respiratory disease in general since chronic continuous hypoxia is also associated with increased muscle fatigue.

Obstructive sleep apnoea (OSA) is a common respiratory disorder [1]. Its effects on health are widespread, including deleterious effects on cardiovascular, respiratory, endocrine, muscle, brain and haematological function [2]. In OSA, the upper airway collapses during inspiration, during sleep causing apnoea. Normally, collapse is prevented by contraction of a large number of upper airway muscles that stiffen and/or dilate the airway and when the airway does collapse, it is the contraction of these muscles that re-opens the airway [3]. Although the causes of OSA are multifactorial, the function of these upper airway muscles plays a crucial role in the pathogenesis of the condition, hence the importance of studies aimed at understanding their anatomy, physiology and pathophysiology.

During the episodes of obstruction, the levels of oxygen in the arterial blood decreases and when the airway re-opens, the hypoxia is alleviated. Therefore, OSA is associated with intermittent hypoxia or asphyxia, the combination of hypoxia and hypercapnia (raised carbon dioxide levels). Some of our work has focussed on the hypothesis that intermittent hypoxia and asphyxia adversely affect upper airway muscle function, thereby creating a vicious cycle that makes the condition worse. This hypothesis was developed based on the fact that upper airway muscle morphology was reported to be abnormal in the English bulldog, an animal model of sleep apnoea [4] and in OSA patients [5]. It was also based on the knowledge that chronic continuous hypoxia can affect skeletal muscle structure and function so it occurred to us that perhaps the changes in upper airway muscle structure observed in humans and dogs with OSA were an effect rather than a cause of the condition i.e. that perhaps intermittent hypoxia and/or asphyxia cause changes in upper airway muscle structure and therefore in function. We have tested this hypothesis by using a rat model of OSA whereby the animal is exposed to cycles of changing inspired oxygen or oxygen and carbon dioxide levels for 8 hours per day for several days or weeks in order to mimic the chronic intermittent hypoxia and asphyxia of human OSA. What we found was that chronic intermittent hypoxia and asphyxia did indeed affect upper airway muscle morphology and physiology. However, the effects on structure were minor but there was a consistent increase in muscle fatigability [6,7] and this was also true for limb muscles and for the diaphragm muscle [8]. More recently, we have identified a slow to fast fibre type transition (that favours increased fatigability) in diaphragm muscle following chronic intermittent hypoxia treatment [9]. Somewhat similar findings have been also reported elsewhere [10] and our data are further corroborated by the reported effects of chronic continuous hypoxia which, although to some extent equivocal, appear to be broadly similar. Thus, the chronic sustained hypoxia of chronic obstructive pulmonary disease is associated with decreased skeletal muscle aerobic capacity [11], slow to fast fibre type transition [12], and greater muscle fatigue [13]. Furthermore, the chronic hypoxia of altitude causes a decrease in human muscle aerobic capacity [14], and mitochondrial function [15] and chronic hypobaric hypoxia in rats increases limb muscle [16] and upper airway muscle [17] fatigue. Of interest, the diaphragm muscle is relatively tolerant of sustained hypoxia compared to upper airway and limb muscles [16-20]. Although in general we have seen only minor changes in muscle structure in response to intermittent hypoxia, the earlier studies, referred to above, of upper airway muscle morphology in the English bulldog [4] and in OSA patients [5] showed a fibre type transition from slow to fast for the dog and greater anaerobic capacity in OSA patients. Both of these effects would likely result in increased fatigability. Clearly, the reduced endurance caused by chronic intermittent hypoxia and asphyxia has important implications for OSA since greater fatigability of the upper airway muscles would make the upper airway more prone to collapse and create a positive feedback that would exacerbate the condition.

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Received September 19, 2013; **Accepted** September 19, 2013; **Published** September 21, 2013

Citation: Bradford A, O'Halloran KD (2013) Obstructive Sleep Apnoea, Intermittent Hypoxia and Respiratory Muscle Structure and Function. Anatom Physiol 3: e123. doi: 10.4172/2161-0940.1000e123

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We have also looked at the mechanism of these effects. The fact that the changes occurred not just in respiratory muscles but also in limb muscles is evidence that these effects are not due to altered neural drive to the muscles caused by the hypoxia/asphyxia. In our model, there would be greater neural activation of the upper airway muscles and diaphragm caused by the hypoxic/asphyxic respiratory stimulus but this would not be true of the limb muscles. This suggests that the hypoxic/asphyxic effects are at the level of the muscles themselves. We were struck by the parallel between ischemia-reperfusion and intermittent hypoxia/asphyxia. Ischemia followed by reperfusion can cause tissue injury due to free radical generation caused by the re-oxygenation [21]. We hypothesised that the systemic hypoxia/re-oxygenation of intermittent hypoxia causes oxidative stress i.e. the generation of reactive oxygen species that in turn cause the adverse effects on muscle function. We tested this hypothesis by exposing rats to intermittent hypoxia and to pro- and anti-oxidants. We found that even in normoxic rats, antioxidants improved force generation and endurance of upper airway muscles [22]. Furthermore, we found that chronic treatment with an antioxidant (a superoxide scavenger) prevented the reduction in force generation in upper airway muscle caused by chronic intermittent hypoxia and interestingly, this reduction in force could be reversed by acute administration of the antioxidant [23]. We also found that treatment with a pro-oxidant exacerbated the loss of endurance in upper airway muscle caused by chronic intermittent hypoxia [24]. However, we have found that the increase in upper airway muscle fatigability caused by chronic continuous hypoxia during early development was not prevented by antioxidant treatment [17], despite the fact that chronic continuous hypoxia has been shown to generate free radicals [25].

To summarise, it would appear that in general, both chronic sustained hypoxia and chronic intermittent hypoxia cause a reduction in skeletal muscle endurance. This maladaptive response has obvious relevance to conditions of intermittent hypoxia such as sleep apnoea and to conditions of continuous hypoxia such as respiratory disease in general since greater respiratory muscle fatigability is likely to exacerbate the underlying condition. Oxidative stress is implicated in the underlying mechanism since some of these deleterious effects can be prevented by treatment with free radical scavengers.

Acknowledgements

Funded by the Health Research Board Ireland, the Irish Research Council for Science, Engineering and Technology, Royal College of Surgeons in Ireland, University College Dublin Ireland, the Charitable Infirmary Charitable Trust Ireland, Higher Education Authority Ireland and the Physiological Society.

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