Journal of Thermal Biology 38 (2013) 214–217

Contents lists available at SciVerse ScienceDirect

Journal of Thermal Biology

journal homepage: www.elsevier.com/locate/jtherbio

Lung perfusion is affected by chronic cold exposure

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ARTICLE INFO

Article history:
Received 8 September 2012
Accepted 1 February 2013
Available online 11 February 2013

Keywords:
Cold
Perfusion
Lung
Rabbit
Radionuclide
^{99m}Tc MAA

ABSTRACT

Background/Aim: The Respiratory system can be affected by exposure to cold. It is well known that acute cold exposure induces asthmatic attacks. However, the influence of chronic cold environment exposure on lung perfusion and the pulmonary circulation was not studied in any previous study. Therefore this study was designed to investigates the effects of chronic cold exposure on lung perfusion using radionuclide study.

Methods: New Zealand White rabbits were used in these experiments. The rabbits were kept in the cold room (4 °C) for 7 weeks. Lung perfusion scintigraphy was performed at the end of this period. Each rabbit was injected with 74 MBq (2 mCi) technetium-99m macroaggregated of albumin (^{99m}Tc MAA). Perfusion studies were done using Gamma camera equipped with a low energy, high resolution, parallel hole collimator interfaced with a computer. Static images were obtained 5 min after administration of the radiotracer. Static images were acquired include anterior/posterior (Ant/Post), right anterior oblique/left posterior oblique (RAO/LPO), right lateral/left lateral (RLat/LLat), right posterior oblique/left anterior oblique (RPO/LAO).

Results: Rabbits chronically exposed to cold had lesser lung perfusion than controls using radionuclide perfusion study. The lung counts of chronic cold exposure (4 °C) for 7 weeks on rabbit lung perfusion for 5 min was $64 \pm 4\%$. ($n=6$, $^{***}P<0.001$).

Conclusions: Our results indicate that chronic cold exposure decreased pulmonary circulation and lung perfusion in normal subjects. Therefore chronic cold exposure might worsen some diseases that are affected by cold such as asthma.

1. Introduction

The bronchial arteries originate from the aorta and wind around the airways to form an adventitial or peribronchial plexus (Deffebach et al., 1987). The peribronchial plexus sends branches down through the airway smooth muscle layer to form a submucosal plexus beneath the epithelium and then empties into the pulmonary vein (Deffebach et al., 1987). Pulmonary arteriovenous anastomoses (AVA) known to exist and function in the fetus are also present and function in adult human being and are controlled by oxygen tension. Various un-physiological status (atelectasis, liver disease, etc.) expand their function and act as a blood conduit resulting in compromised oxygenation. Effect of temperature on the AVA is not reported in the literature (Lovering et al., 2007). Blood flow to the trachea, on the other hand, is supplied by the tracheal arteries and veins. The bronchial and tracheal vascular bed serves at least three important physiological functions: (1) nourishment of the airway wall, (2) conditioning of inspired air (warming and humidification), and (3) defense and clearance of the airways (Wagner, 1998). Some propose that defects in bronchial vascular function contribute to asthma, particularly exercise, cold, and dry air-induced bronchoconstriction (Wagner, 1998). Bronchial arteries receive excitatory sympathetic and inhibitory parasympathetic innervation (Bruner and Schmidt, 1946; De Letona et al., 1961). In contrast to most other vascular smooth muscle beds in which temperature is maintained at 37 °C, bronchial vascular temperature is expected to vary considerably, particularly during exercise. This is because heat is transferred to the inspired air to warm it to physiological temperatures; heat is also lost from the airway wall during the process of humidification of the inspired air. The magnitude of this heat transfer increases substantially during inspiration of very cold air or during exercise. Until now, there have not yet been any direct measurements of the temperature of blood coming out of the bronchial perfusion. However, measurements have been made of the airstream at various points within the lungs: the average temperature in the trachea can be 32 °C during quiet breathing of room air and drop to 29 °C and 20 °C during increased ventilation with room air or frigid air, respectively (McFadden et al., 1985); corresponding temperatures in the subsegmental bronchi can be

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http://dx.doi.org/10.1016/j.jtherbio.2013.02.001

34 °C and less than 30 °C, respectively (McFadden et al., 1982, 1985; Gilbert et al., 1987). It was also proven that warming of inspired air in cold-exposed rabbits is accomplished in the nasal cavity. The nasal temperatures decreased and temperature gradients from proximal to distal parts of the concha increased in cold-exposed rabbits (Caputa, 1979).

Mustafa et al., 1999a, 1999b showed that cooling induces contraction in ovine tracheal and bronchiolar smooth muscle. The contractions is mainly due to intracellular calcium. This is brought about by release of calcium from intracellular storage sites and inhibition of calcium extrusion and sequestration of calcium. Khadadah et al., 2011 proved that even acute cold exposure can decrease the perfusion to the lung. Lung scintigraphy allows imaging of ventilation and perfusion distribution and assessment of regional lung function in lung disease (Argyros et al., 1993). Lung scintigraphy is used primarily to identify pulmonary embolism, pneumonia, and obstructive lung disease (Bruner and Schmidt, 1946; Arowolo and Eyre, 1980; Baile et al., 1986, 1987; Argyros et al., 1993). It is well known that pulmonary ventilation and perfusion are interactive to each other. This means that arterial blockade can lead to bronchoconstriction and obstructive airway disease can change the lung perfusion as well.

The aim of our study is to examine the effect of chronic cold exposure on lung perfusion. The influence of chronic cold exposure to lung perfusion has been not yet studied.

2. Materials and methods

2.1. Experimental animals

Twelve adult male New Zealand White rabbits of the same age (10 weeks) weighing 3–3.5 kg were studied. All animals were kept on adequate food and water in our animal house facility. Marginal veins in both ears were connected to butterfly needles. One vein was used for anesthesia and the other vein was used for obtaining blood samples. Each rabbit was anaesthetized with ketamine (40 mg/kg i.v). The experiments were performed in accordance with guidelines approved by the Institutional Animal Care and Use Committee of Kuwait University.

The Twelve Rabbits were divided into two groups, 6 rabbits each, (1 rabbit per cage). The first group were kept at room temperature, 25 °C, served as controls (group 1). while the second group, age-matched littermates rabbits were kept in the cold room at 4 °C for a period of 7 weeks (group 2). Rabbits in both groups were fed and had access to water throughout the duration of the study. The study was approved by the Institutional research committee.

2.2. Radionuclide imaging

The investigation was done using the radiopharmaceutical agent which can be considered as a new tool in this kind of research leading to conclusive results. At the end of 7 weeks, lung scintigraphy was performed for the control rabbit group and for the chronically exposed to cold group. Each radionuclide study was performed using 74 MBq (2 mCi) technetium-99m macroaggregated of albumin (^{99m}Tc MAA). Studies were done using Gamma camera (Meridian System, T55B-1473) equipped with a low energy, high resolution, parallel hole collimator interfaced with a dedicated computer. Rabbits were positioned after anesthesia in the supine position to minimize the gradient. ^{99m}Tc MAA is injected slowly intravenously and lodges in percapillary arterioles. Injection of the tracer is done while the rabbit was in supine position. Static images were acquired include anterior/posterior (Ant/Post), right anterior oblique/left posterior oblique (RAO/LPO), right lateral/left lateral (RLat/LLat), right posterior oblique/left anterior oblique (RPO/LAO). Acquisition was done for 5 min using 256 × 256 matrix. Region of interests (RIO) s are drown on the all views and perfusion is calculated in both groups. The comparison of pulmonary blood flow distribution was done between the control lungs and after cold exposure.

Perfusion scintigraphy is most commonly achieved by microembolization with ^{99m}Tc-labeled macroaggregates of human albumin (MAA). Lung perfusion scintigraphy with MAA depends on the principle that ^{99m}Tc MAA particles in the bloodstream are trapped in the lung at first passage (Taplin and MacDonald, 1971; Kumar and Parker, 2001), causing temporary "micro-embolisms" (Wagner, 1995; Weiss, 1996). The number of the trapped particles is in direct proportion to the local rate of blood flow (Tow et al., 1966). The mechanism of localization of particles in the lung is purely a mechanical process, called capillary blockade. Following their rapid accumulation in the lung, MAAs are mechanically and enzymically degraded, and phagocytosed in the liver (Chandra et al., 1973). For scintigraphic imaging, the MAAs are labeled with the nuclide technetium-99m (Tc-99m). This agent has a biological half-life in the lungs between 6–8 h. The uptake of MAA is the basis for ^{99m}Tc MAA scintigraphy. Following elimination from the lung (half-time for residence 1–24 h) (Monroe et al., 1974; Darte et al., 1976; Robbins et al., 1976; Neumann et al., 1980; Malone et al., 1983; Wagner, 1995) the radioactivity is excreted, via the liver and kidneys, in the urine (Chandra et al., 1973; Robbins et al., 1976; Malone et al., 1983).

2.3. Statistical analysis

Data are presented as mean ± (SEM) of number of rabbits used in the experiments (n). Where necessary, differences between two mean values were compared using Students-t-test paired or unpaired as appropriate. Where multiple comparisons were necessary one way analysis of variance (ANOVA) was used followed by Student–Newman–Keuls test. The difference was assumed to be significant at $P < 0.05$.

3. Results

The comparison of pulmonary blood flow perfusion between the control lung and after 7 weeks cold exposure was done using radionuclide perfusion study. Images of lung perfusion before and after cold exposure proved that blood perfusion was significantly decreased as shown in Figs. 1 and 2. All the static images include Ant/Post, RAO/LPO, RLat/LLat and RPO/LAO for control and after 7 weeks cold exposure, showed lesser lung perfusion for cold exposure than controls. These results illustrated that lung image can be acquired at any position during cold exposure to give the same results.

The lung count of chronic cold exposure (4 °C) for 7 weeks on rabbit lung perfusion for 5 min was 64 ± 4% of control. The mean ± SEM of 6 experiments was 4190 ± 43 and 2795 ± 25 K counts for control and after cold exposure respectively, ($n=6$, $^{***}P < 0.001$). Therefore it is very clear that chronic cold exposure changed the blood perfusion to the lung.

4. Discussion

This present study proved that lung perfusion was significantly decreased after chronic cold exposure. This decrease can contribute in the severity of respiratory diseases. Cold-related respiratory symptoms are common, especially among people suffering from respiratory diseases (e.g. asthma, COPD). Cold-related respiratory symptoms

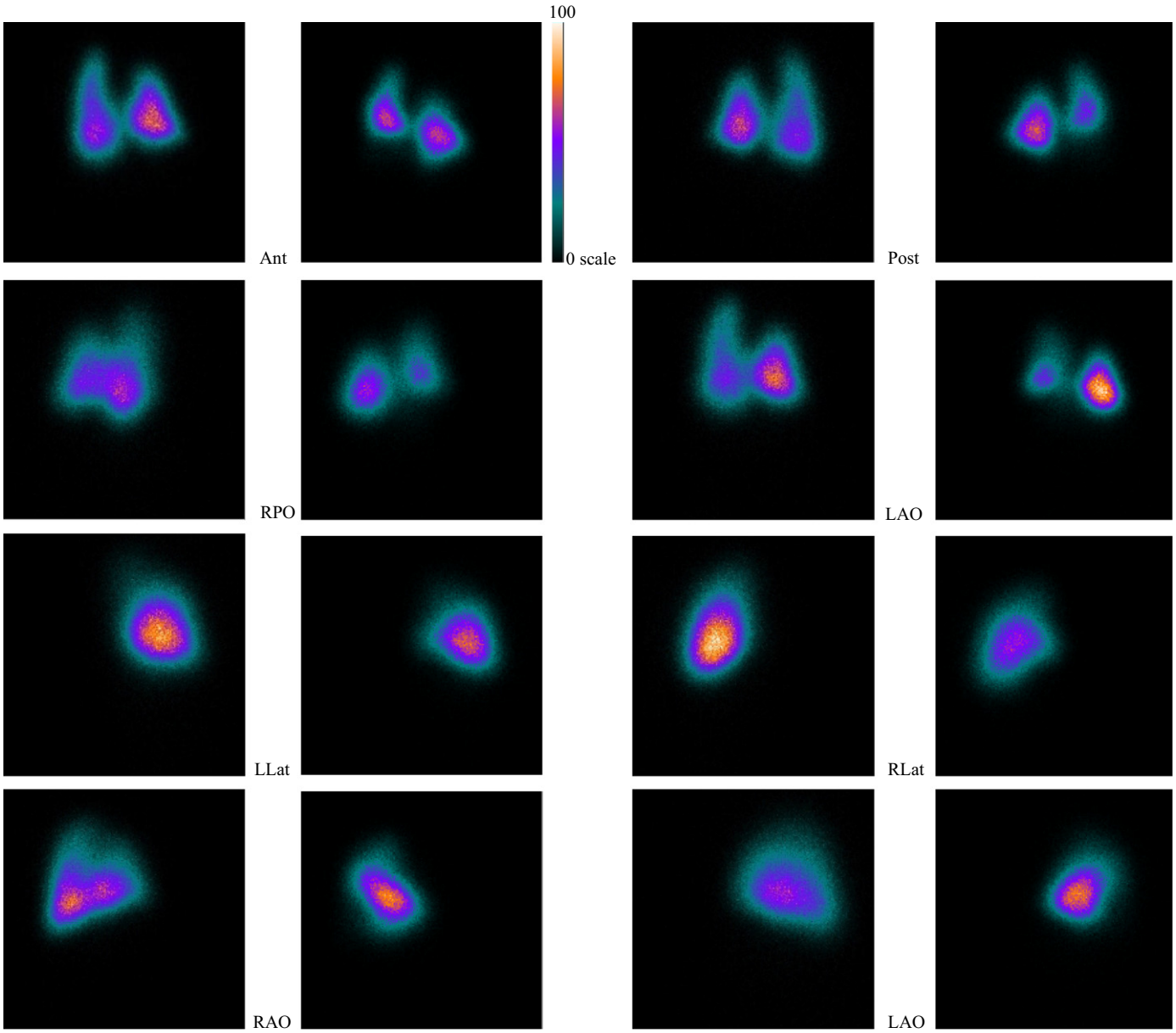

Fig. 1. Images of a rabbit lung perfusion for 5 min for control and chronic cold exposure to 4 °C for 7 weeks. Static images were acquired include anterior/posterior (Ant/Post), right anterior oblique/left posterior oblique (RAO/LPO), right lateral/left lateral (RLat/LLat), right posterior oblique/left anterior oblique (RPO/LAO).

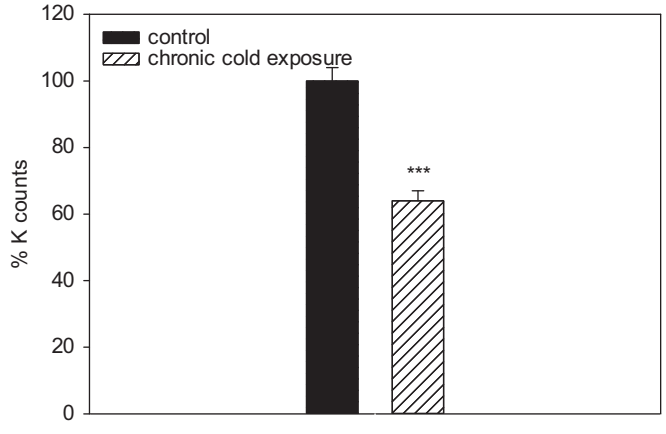

Fig. 2. Effect of chronic cold exposure (4 °C) for 7 weeks on rabbit lung perfusion for 5 min. The mean ± SEM of 6 experiments. ***$P < 0.001$.

start to emerge at relatively low temperatures. In cold climates, the cold-related symptoms may have an impact on the health-related quality of life (Harju et al., 2010). Chronic cold exposure elicits several effects on the respiratory system. Pulmonary mechanics are compromised by bronchoconstriction, airway congestion, secretions and decreased mucociliary clearance. These responses are active in cold- or exercise-induced asthma. The primary ventilatory effect of cold air is to decrease baseline ventilation and respiratory chemosensitivity. Although these responses provide significant protection against heat loss in many animals, the effect in humans is minimal. Chronic exposure to cold environment results in morphological changes such as increased numbers of goblet cells and mucous glands, hypertrophy of airway muscular fascicles and increased muscle layers of terminal arteries and arterioles (Giesbrecht, 1995). The bronchial circulation is important for the supply of oxygen and nutrients to the various cell types of the airways (epithelium, smooth muscle, and innervation), and it has a key role in the warming and humidification of inspired air (Deffebach et al., 1987). The bronchial circulation can

also influence airflow in several ways. For example, vasodilation of this vascular bed increases the thickness of the mucosa and the stiffness of the airway wall (Bruner and Schmidt, 1946; Laitinen et al., 1986; Corfield et al., 1991).

Abnormal communications between blood vessels of the lung may also be found in a variety of acquired conditions. Right-to-left shunting as a result of communications between pulmonary arteries and pulmonary veins has been reported in hepatic cirrhosis, and less commonly in schistosomiasis, mitral stenosis, trauma, actinomycosis, Fanconi's syndrome, and metastatic thyroid carcinoma. Communications between bronchial arteries and pulmonary arteries, causing left-to-right shunt, can develop in chronic inflammatory conditions such as bronchiectasis (Gossage and Kanj, 1988). Anastomoses between arteries and between veins result in a multitude of arteries and veins. Such anastomoses serving as backup routes for blood to flow if one link is blocked or otherwise compromised, but may also occur pathologically. Arteriovenous anastomosis is a connection between an artery and a vein. Pulmonary arteriovenous malformations are caused by abnormal communications between pulmonary arteries and pulmonary veins, which are most commonly congenital in nature. Radionuclide Perfusion Lung Scanning can be affected by pulmonary arteriovenous. In subjects without intrapulmonary shunt, peripheral intravenous injection of ^{99m}Tc MAA results in filtering of these particles by the capillaries of the lung. However, anatomic shunts with dilated pulmonary vascular channels will allow passage of these particles through the lungs, and subsequent filtering by capillary beds in other organs such as brain and kidneys. Hypoxemia is often observed in patients with liver cirrhosis which may be attributable to the presence of intrapulmonary shunt due to dilated peripheral pulmonary vessels and small arteriovenous communications. This intrapulmonary vascular dilation can be detected by ^{99m}Tc MAA scintigraphy. (Hosono et al., 2002).

In conclusion, this study has shown that the lung perfusion is significantly decreased during chronic cold exposure and this can be attributed to vasoconstriction of the blood vessels in the lungs to provide protection against heat loss. Therefore chronic cold exposure can be assumed a cause of increased acute asthma attacks and probably other pulmonary disorders.

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