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Heating-induced contraction in airways smooth muscle: A possible causative factor of exercise-induced bronchoconstriction

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ABSTRACT

Asthmatic patients often suffer from bronchoconstriction or asthma following breathing hot air or exposure to exercise due to raises the core body temperature. However, the direct effect of heating airways has not been studied yet. The aim of this study is to investigate the effect of heating on tracheal and bronchiolar smooth muscles. Isolated ovine tracheal strips and bronchiolar segments preparations were suspended in organ baths containing Krebs' solution for isometric tension recording. Tissues responses were examined during decreasing and elevating baths temperature (20 °C, 40 °C–45 °C and 50 °C). Cooling or heating induced rapid and reproducible contractions proportional with decreasing or increasing temperature respectively in tracheal and bronchiolar preparations. On reset to 37 °C the tone returned rapidly to basal level. Changing the bath's temperature from 37 °C to 20 °C or to 40 °C and 45 °C for tracheal strips or to 45 °C and 50 °C for bronchiolar segments induced contractions in both preparations. Changing the temperature below or above the normal body temperature (37 °C), leads to airways contractions. Heating induced contractions in tracheal and bronchiolar smooth muscle proportional to the heating temperature. Therefore, breathing hot air or elevation of body core temperature due to exercise can be considered possible causative factor of heating- or exercise-induced bronchoconstriction.

1. Introduction

Hot weather is well known in Arabian Gulf countries and many other places all over the world. In these countries, although the temperature can exceed 60 °C during summer, humans can survive. High temperature can trigger asthma symptoms in some people, leading to coughing and shortness of breath, and the reason is not known. This condition has been reported but the pathophysiology of it is not entirely understood, although there are many proposed mechanisms are released. Some studies related the bronchoconstriction induced by increasing airway temperature in asthmatic patients to circulating catecholamines (Barnes et al., 1981), or to cholinergic reflex pathway (Hayes et al., 2012; Stang et al., 2016), or activation of the transient receptor potential vanilloid type 1 (TRPV1) (Ruan et al., 2005). Other studies explained that increasing of asthma severity is due to exhaled hot air and the involvement of vascular endothelial growth (Ntontsi et al., 2018). Many asthmatic experience asthma symptoms in times of high heat and humidity. They explained that the extreme temperature can cause air to become stagnant, trapping pollutants in the air, which can cause asthma (D'Amato, 2002; D'Amato et al., 2016; D'Amato et al., 2015). The term exercise induced bronchoconstriction (EIB) describes the acute transient airway narrowing that occurs during or after exercise in 10–50% of elite athletes (Rundell and Jenkinson, 2002). This state has been shown in a range of sporting activities. It has been shown that aerobic exercise in dry air is causing airway hyperresponsiveness and can lead to asthma (Rundell and Sue-Chu, 2013) It was reported that hyperventilation during exercise causes a loss of heat and drying of the airways, leading to dehydration of the airways cells and increased intracellular osmolality. It stimulated the release of inflammatory mediators which caused bronchoconstriction (Bonini and Craig, 2008; Carlsen et al., 2008; Del Giacco et al., 2001; Anderson and Daviskas, 2000). Other researchers suggest that it is related to airway epithelial injury from breathing poorly conditioned air or a high volume of irritant gases or particles (Anderson and Kippelen, 2008). EIB commonly occurs several minutes into or following an exercise event (Del Giacco et al.,2015; Molis and Molis, 2010; Smoliga et al., 2016; Storms, 2003). Respiratory heat and water loss have been suspected as the precursor to exercise induced asthma (Kyle et al., 1992; Freed et al., 1994). It is also declared that the severity of bronchoconstriction is related to water content of inspired air and level of ventilation achieved and sustained

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(Rundell et al., 2015). The air temperature and water content of inspired air play an important role in EIB. In particular, dry air appears to promote a substantial inflammatory response among these patients. Some asthmatics find that any form of physical activity starting from stroll or climbing the stairs to Zomba class or a game of tennis can trigger asthma symptoms or an asthma attack.

From the previous literatures, there is no study examined the direct effect of heating on airways. Therefore, our aim is to study the effect of heating on ovine tracheal and bronchiolar smooth muscle, and correlate the effect to the elevation of core body temperature due to exercise.

2. Materials and methods

2.1. Preparation of tracheal strips and bronchiolar segments

Six young female Merino sheep were used for this study. The trachea together with the lung of Merino sheep were obtained from a slaughter house, placed in chilled Krebs' solution of the following composition (mM): (NaCl 118, MgSO4 1.2, KCl 5.9, glucose 11.1, NaHCO3 26, KH2PO4 1.2, and CaCl2 2.2 in mM concentration) at pH 7.4, and transported to the laboratory within 30 min A piece of the trachea was cleaned of adhering adipose and connective tissue and opened longitudinally through the cartilage rings diametrically opposite the trachealis muscle. Thereafter it was pinned flat on a cork board and strips of smooth muscle 10 mm in length and 5 mm in width were dissected free from the underlying cartilage. In some experiments, the epithelium and submucosa were carefully removed from the strips leaving smooth muscle only. An incision was made in the parenchyma and small bronchioles 3–4 mm in diameter were dissected out without damage to the epithelium and cut into 5-mm ring segments. In some experiments, the epithelium was removed by gently rubbing the luminal surface with a wooden probe. Preparations were suspended in 20-ml organ baths containing Krebs' solution, maintained at 37 °C and aerated with 95% O_2 and 5% CO_2. Isometric contractions were recorded by computerized, automated isometric transducer system (Schuler organ bath 809; Hugo Sachs Electronik, March-Hugstetten, Germany) which connected to a Gould recorder (Gould Instrument Inc., Cleveland, OH, USA), Tracheal strips were suspended at a preset-tension of 2 g and bronchiolar rings to 1 g. The tracheal and bronchial preparations were allowed to equilibrate for 60 min, during which time they were washed twice. Contractile responses were calculated as % to carbachol effects.

2.2. Cooling and heating protocol

The organ bath temperature was reduced or increased using a thermostated supply bath (Haake F3, Fisons, Germany) that had been set to the appropriate temperature. It took 2–3 minutes to reach the desired temperature, from 37 °C to 20 °C or 40 °C and 45 °C for tracheal strips or to 20 °C or to 45 °C and 50 °C for bronchiolar segments. Each cooling or heating period was maintained until a peak response had leveled off.

2.3. Drugs

Carbachol hydrochloride was obtained from Sigma chemicals, St Louis, MO, USA.

2.4. Calculations

Data are calculated as the mean of (n) experiments ± SEM, where n is the number of animals used. The differences between two mean values were analyzed using Student's-t test paired. The difference was considered significant at $P < 0.05$.

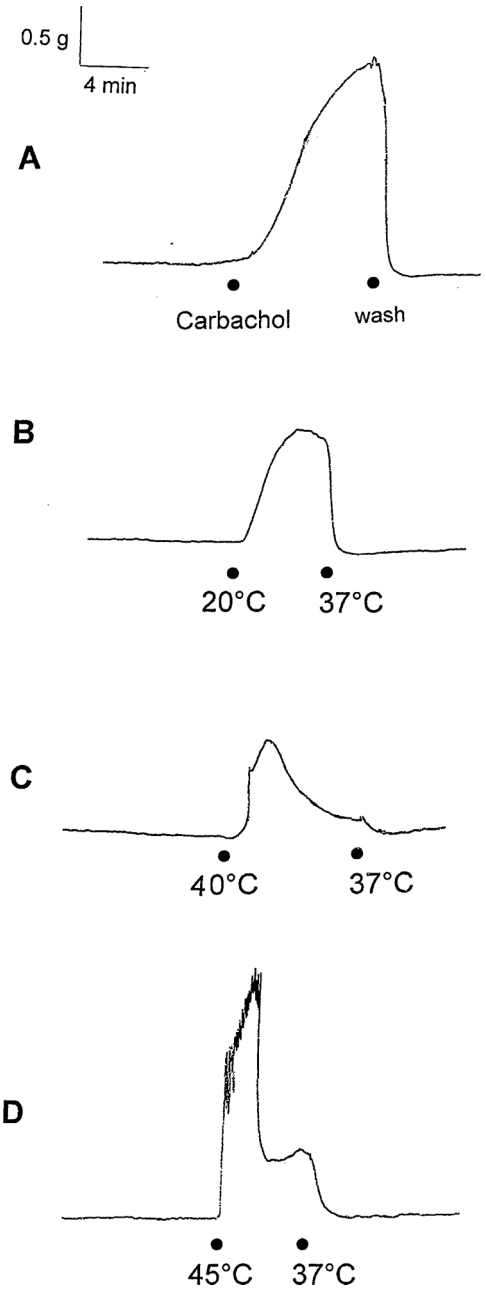

Fig. 1. Original recording of an isolated ovine tracheal strip at 37 °C showing the contractile effects to: A) carbachol (1 nM); B) 20 °C; C) 40 °C; D) 45 °C.

3. Results

3.1. Carbachol-induced contraction

All the tracheal strips and bronchial ring segments preparations maintained a consistent steady baseline. Carbachol (1 nM and 50 nM) induced contractions of tracheal strips and bronchiolar rings respectively, as shown in all Figs. 1 & 3 .

3.2. Cooling-induced contraction (CIC)

Lowering the bath temperature induced rapid contractions in tracheal and bronchiolar preparations. Figs. 1 and 3 are showing typical traces representing 20 °C-induced contractions and when the temperature was reset to 37 °C, the tone rapidly returned to the basal levels of the trachea and bronchiole respectively.

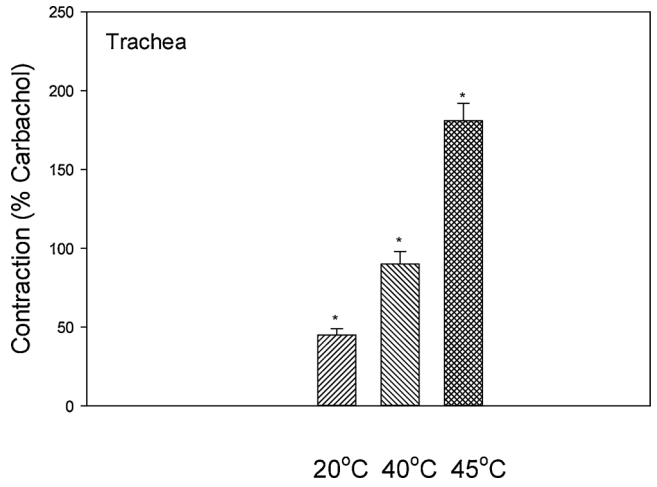

Fig. 2. The contractile effects of 20 °C; 40 °C and 45 °C; as % to carbachol (1 nM) on isolated ovine tracheal strips. Each bar represents the mean ± S.E.M. of 6 animals. *P < 0.05.

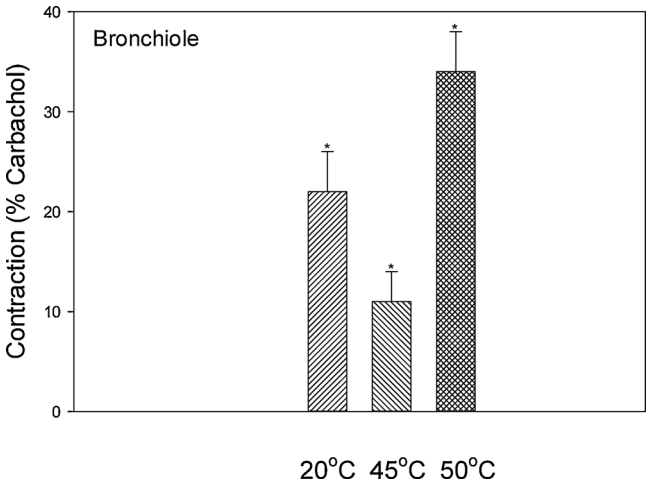

Fig. 4. The contractile effects of 20 °C; 45 °C and 50 °C; as % to carbachol (50 nM) on isolated ovine bronchiolar segment. Each bar represents the mean ± S.E.M. of 6 animals. *P < 0.05.

3.3. Heating-induced contraction

Before heating, all preparations maintained a stable baseline. Elevation of the organ bath temperature from 37 °C to 40 °C and 45 °C induced rapid contractions in tracheal strips. Raising the temperature from 37 °C to 45 °C then to 50 °C induced rapid increase in tension that was proportional to the bath temperature in bronchiolar segment. A typical original trace represents carbachol, cooling to 20 °C and heating to 40 °C and 45 °C-induced contractions and when temperature was reset to 37 °C, the tone rapidly returned to basal level is shown in Figs. 1 & 3 .

Figs. 2 and 4 are representing the average of the contractions due to cooling to 20 °C and heating to 40 °C or 45 °C for tracheal strips and to 45 °C or 50 °C for bronchiolar rings.

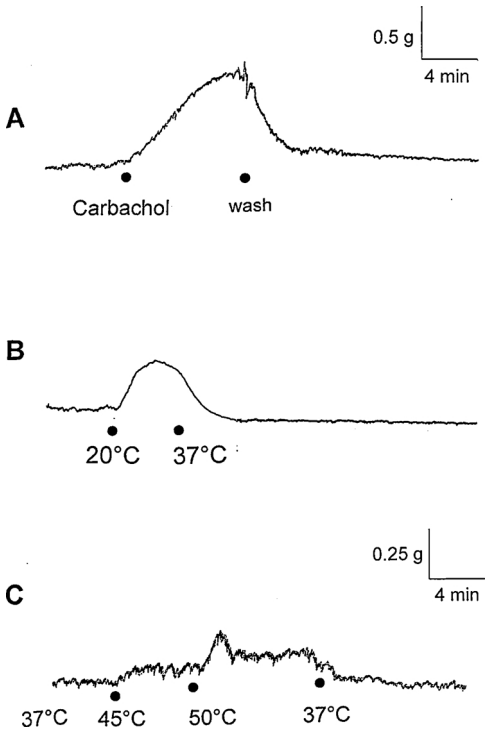

Fig. 3. Original recording of an isolated ovine bronchiolar segment at 37 °C showing the contractile effects of: A) carbachol (50 nM); B) 20 °C; C) 45 °C; and 50 °C.

3.4. Role of epithelium

Removal of the epithelium did not significantly reduce the contractile response to heating in the tracheal and bronchiolar preparations. Epithelial removal however, potentiated carbachol-induced contractions in the trachea, consistent with our previous study (Mustafa et al., 1999a) and indicating that the smooth muscle was not damaged during stripping.

4. Discussion

The study showed that elevating the bath temperature to 40 °C, 45 °C or 50 °C induced contractions of tracheal and bronchiolar smooth muscles. The contractions were rapid and reproducible and are not epithelium-dependent. (Mustafa et al., 2013; 2015; 1999a; 1999b; 1999c; Khadadah et al., 2011. proved that lowering the temperature below 37 °C induced tracheal and bronchiolar contractions proportional to the cooling temperature. We choose 20 °C as a cooling temperature in the present study, because it induced submaximal contraction according to our previous publications. It is clear that changing the temperature above or below 37 °C induced contraction in tracheal and bronchiolar smooth muscles. Therefore, cooling or heating induced constrictions in respiratory system. Airway narrowing can occur during or immediately after exercise, which is known as exercise-induced bronchoconstriction (EIB) or exercise-induced asthma according to the severity. The prevalence of EIB varies from 5 to 20% in the general population. While it is around 90% of patients with symptomatic asthma (Parsons and Mastronarde, 2005; Boulet and O'Byrne, 2015). In addition, the prevalence of EIB appears to be higher among elite athletes (Del Giacco et al., 2015; Fitch, 2012; Fitch et al., 2008; Moreira et al., 2011). Athletes undergoing high physical exercise can fall victims to hyperthermia by producing metabolic heat at a high rate, even when environment is not very hot. Children and adolescents are more frequently affected than adults (Garcia-Larsen et al., 2016; Gotshall, 2002; Grzelewski and Stelmach, 2009). Children are more susceptible to heat exhaustion or heat stroke than adults. They produce more metabolic heat per unit mass, and are less able to dissipate heat because of a relatively low capacity to produce sweat. More than 36% of 10-years old asthmatic children showed exercise induced asthma, while 8% induced EIB in the entire population-based birth (Lodrup Carlsen et al., 2006).

When we start exercising, our muscles quickly deplete stored energy. To make more energy, the metabolism process uses oxygen to break down glucose and give the muscle the energy they need to

contract repeatedly. Each muscular contraction produces heat. Extra heat raises the core body temperature which can easily reach above 40 °C. Our body has a system for heat loss depending on different factors. Exposure to heat stress as a result to hyperthermia or being in a hot environment, is accompanied by an increase in pulmonary ventilation (Zila and Calkovska, 2011). Some in-vivo studies for human or animals showed that breathing hot air or hyperthermia can triggered bronchoconstriction (Aitken and Marini, 1985; Hayes et al., 2012; Lin et al., 2009). Climate change and heat waves increase morbidity and mortality in asthmatic patients (Witt et al., 2015). Our results link the high body temperature and the occurrence of bronchoconstriction directly on the smooth muscle of trachea and bronchiole.

5. Conclusion

Heating induced contractions in tracheal and bronchiolar smooth muscle proportional to the heating temperature. Therefore, elevation of body core temperature due to exposure to hot weather or exercise can be considered possible causative factor of exercise-induced bronchoconstriction.

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