Cardiorespiratory Parameters and Respiratory Reflexes in Rabbits During Hyperthermia

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Summary
The effects of different body temperature (BT) on the respiratory and cardiovascular parameters and respiratory reflexes were studied in 33 anaesthetized adult rabbits. Hyperthermia elicited panting with mean panting respiratory rate 199±14 x min⁻¹ in all anaesthetized rabbits. Significant correlations between BT and frequency of breathing (positive), heart rate (positive) or tidal volume (negative) were found. Cooling was accompanied by considerable arterial hypotension. Duration of the Hering-Breuer reflex (HB) was reduced by the rise of BT. Intensity of the reflex (assessed as the ratio of the apnoeic pause to the mean duration of the previous 5 breaths) was unchanged up to the body temperature eliciting panting (41.15±0.08 °C) when it was greatly diminished. Defensive airway reflexes were also changed in hyperthermia. The duration as well as the intensity of nasal apnoea (Kratschmer's reflex) and laryngeal chemoreflex apnoea were decreased. The intensities of respiratory efforts in sneezing and laryngeal coughing were reduced. The expulsive reactions evoked by mechanical stimulation of the larynx were replaced by very shortlasting inhibition of breathing during panting. The results indicate that reflex control of breathing via the Hering-Breuer reflex and the ability to eliminate irritants from the airways are diminished during hyperthermia and panting in anaesthetized rabbits.

Key words

Introduction
Inflation of the lungs inhibits inspium and promotes expirium by stimulation of slowly-adapting pulmonary stretch receptors. These effects are known as Hering-Breuer inflation reflex (HB reflex). A next group of respiratory reflexes from the airways is represented by defensive reflexes aimed to prevent the penetration of different harmful agents into the lungs or to eliminate them. They include Kratschmer's apnoeic reflex (nasal apnoea), laryngeal chemoreflex, sneezing, coughing and the expiratory reflex (Körpáš and Tomori 1979).

An increase in body temperature (BT) evokes a high frequency of respiration at small tidal volumes with thermoregulatory effects – thermal polypnoea – panting. It has been postulated that hyperthermia may induce significant changes in respiratory and cardiovascular control (Widdicombe and Winning 1974, Von Euler and Trippenbach 1976).

The present work was undertaken to obtain further information on the changes of cardiorespiratory parameters and neural control of breathing (the inflation reflex as well as protective and defensive airway reflexes) during a gradual increase in body temperature and the following recovery of the BT to the initial temperature levels in rabbits.

Methods
The experiments were carried out on thirty-three adult rabbits (chinchilla), mean body weight 2.77±0.05 kg under general anaesthesia by sodium pentobarbital (Pentobarbital Spofa, Czechoslovakia) in an introductory dose of 40 mg/kg i.v. and maintenance doses 15 mg/kg/h. The animals were tracheotomized.
Blood pressure in the femoral artery was recorded with the electromanometer LDP 102 (Tesla, Czechoslovakia).

The rabbits breathed room air spontaneously through a tracheal cannula connected with the Fleisch head of a pneumotachograph (UMMT SAV, Bratislava) and via the mainstream sensor of a capnograph (Capnogard, Novametrix, USA) for continuous monitoring of end-tidal CO₂ (ET\textsubscript{CO₂}) with response time less than 75 ms. The tracheal pressure in experiments with the inflation reflex was registered by an electromanometer LDP 165 (Tesla Czechoslovakia) with the flat frequency response up to 60 Hz. Interpleural pressure (Ppl) was recorded by means of an electromanometer LDP 165 through a special cannula. Airflow, tidal volume, tracheal, interpleural and blood pressures were recorded by a multi-channel recorder 6 NEK 4 (RFT, Germany). The frequency of breathing, duration of apnoea and heart rate were calculated from the airflow and blood pressure traces. These values were recorded and evaluated at each change of body temperature (BT) by 0.5 °C during warming or cooling.

Arterial PO\textsubscript{2}, PCO\textsubscript{2}, pH and rectal temperature were also monitored. Blood samples were taken from the femoral artery at each degree of centigrade at different temperature levels. Arterial blood gases and pH were evaluated using a blood gas analyzer BMS-3 (Radiometer, Copenhagen, Denmark) and corrected for actual BT. Rectal temperature was measured with a mercury thermometer at a depth of 6—7 cm.

Ten animals were used for the study of cardiovascular changes and for testing of the Hering-Breuer inflation reflex, 16 rabbits for the study of defensive airway reflexes and 7 rabbits served as controls for the subgroup with defensive airway reflexes.

To test the HB reflex, lungs were inflated with constant positive pressure 1 kPa (Davies \textit{et al}. 1978) up to the moment of the first breath during inflation. Intensity of the HB reflex was assessed as the ratio of the apnoeic pause duration to the mean duration of the previous 5 breaths (Ta/T). The inflation reflex was elicited at each 0.5° at different levels of body temperature during overheating and recovery up to the panting level and during the recovery to the initial values of BT.

Kratschmer's (nasal) apnoeic reflex was elicited by intranasal insufflation of xylol vapours produced by constant airflow through liquid xylol during a constant temperature during overheating up to the panting level and decreased symmetrically with lowered BT (Fig. 1). A significant positive correlation (r=0.92) was found between frequency of breathing and body temperature.
Tidal volume ($V_T$) during quiet breathing at the beginning of the experiment was 21.0±1.2 ml and during panting 7.2±0.5 ml. During recovery of BT, the tidal volume increased more rapidly and was significantly higher than during overheating at the corresponding temperature (Fig. 1). $V_T$ at different body temperature levels negatively correlated with BT ($r = -0.96$).

Pa$_O_2$ at the beginning of experiments was 9.1±0.4 kPa, at maximum BT 10.17±0.4 kPa and during recovery of BT it rose to 12.8±0.7 kPa ($P<0.001$).

Pac$_O_2$ gradually decreased from 3.75±0.18 kPa to 2.45±0.11 kPa ($P<0.01$) during panting. In the course of the recovery of initial BT levels a further decrease to 2.00±0.15 kPa ($P<0.01$) was found. There was a negative correlation between BT and Pac$_O_2$ ($r = -0.94$).

The mean value of arterial pHa at the beginning of the experiment was 7.421±0.022 and during panting 7.424±0.031 ($P>0.05$). During cooling, pH gradually decreased and dropped to 7.275±0.039 ($P<0.02$) after reaching the initial values of BT.

End-tidal CO$_2$ (ETCO$_2$) decreased from 5.08±0.16 kPa during the period of quiet breathing to 2.47±0.17 kPa ($P<0.001$) during panting. After recovery of BT to the initial values, ETCO$_2$ was 2.52±0.23 kPa. In 44% of the overheated animals, an

**Fig. 1**

Frequency of breathing ($f$), volume tidal ($V_T$) and ventilation ($V$) during overheating to 42 °C and during body temperature recovery.

The initial mean value of ventilation ($V, f \times V_T$) was 863±80 ml x min$^{-1}$, during the panting 1371±98 ml x min$^{-1}$ with a positive correlation to BT ($r=0.97$). During cooling, the ventilation gradually increased further mainly due to an increase in $V_T$ (Fig. 1).

**Fig. 2**

Systolic (BP syst.) and diastolic (BP diast.) systemic blood pressure and heart rate (HR) during increasing and decreasing of body temperature in ten anaesthetized rabbits.
increase of the inspiratory fraction of CO₂ during panting was observed (average value 0.44±0.03 kPa). During panting there was no plateau on the ET\textsubscript{CO₂} curve.

**Changes in respiratory reflexes**

The duration of inflation apnoea (T\textsubscript{a}) was reduced with the rise of body temperature and frequency of breathing. At the beginning of the experiments it was 32.9±3.6 s, at 42°C 3.62±1.4 s and on recovery of the initial BT it was 44.0±16.3 s (Fig. 3). The intensity of the Hering-Breuer reflex (T\textsubscript{a}/T) only fell during panting (Fig. 3). During recovery, the duration of inflation apnoea became gradually prolonged and the initial intensity of the HB reflex was restored immediately after the cessation of panting.

**Nasal apnoea and the laryngeal chemoreflex** were also elicitable during hyperthermia, however, their duration as well as their intensity were markedly reduced during hyperthermia (Figs. 4 and 5). The shortest duration of these apnoeic reflexes was at the peak of BT. During the recovery of BT to initial values the apnoea remained significantly shorter when compared to initial values. In the controls (C), the duration and the strength of apnoea did not change significantly (P>0.05) (Figs. 4 and 5).

The mechanical stimulation of nasal mucosa constantly evoked sneezing in every animal also during panting. The mean frequency of expiratory efforts (frequency of attack) in sneezing was 82.5±4.5 x min\textsuperscript{-1} in the group with hyperthermia at the beginning of experiment, 83.3±9.6 x min\textsuperscript{-1} (P>0.05) during panting and 65.3±3.6 x min\textsuperscript{-1} (P<0.01) after return of BT to initial values. In the controls, there was no significant difference of frequency of attack at the beginning of the experiment and in the corresponding intervals to "panting" and "recovery of BT" 74.0±3.5, 67.6±3.1 and 68.6±3.5 x min\textsuperscript{-1}, respectively.

The intensity of sneezing (intensities of efforts and attacks, Fig. 6) was reduced during panting in comparison to the values during normothermia. The evaluated parameters of sneezing did not return to the initial values after recovery of initial body temperature. In control (normothermic) animals, no significant changes were found at the corresponding time intervals.

Mechanical stimulation of the larynx at the beginning of the experiment was followed by forced efforts (laryngeal coughing and/or expiratory reflex) in 93 % of cases. Very shortlasting (1.3±0.1 s) inhibition of breathing was characterized by the dominant type of response (76 % of the stimulations) during panting in contrast to stimulations of the controls without hyperthermia (Fig. 7).

The intensity of laryngeal coughing (Fig. 8) was significantly lower during panting, similarly to that of sneezing. By the return of body temperature, it gradually reached initial values, however, even after return to the original values of BT it remained lower similarly to sneezing. There was no change of the intensity of laryngeal coughing in the controls.
Fig. 4
Duration of nasal apnoea (Ta) and strength of this reflex (Ta/T) in the experimental group (E, n = 16) at the beginning of experiment (38 °C), after reaching the panting level (42 °C) and after recovery of BT (38 °C) as well as at corresponding time intervals (1, 2, 3) in 7 controls (C). Asterisks indicate significant differences, NS - nonsignificant differences, n = number of animals.

Fig. 5
Duration of laryngeal chemoreflex induced apnoea (Ta) and the strength of this reflex (Ta/T) in experimental group (E, n = 16) at the beginning of experiment (38 °C), after reaching the panting level (42 °C) and after recovery of BT (38 °C) as well as at corresponding time intervals (1, 2, 3) in 7 controls (C). Asterisks indicate significant differences, NS - nonsignificant differences.
Fig. 6
The intensity of maximum expiratory (IME\textsubscript{e}) and inspiratory (IME\textsubscript{i}) efforts and the mean intensity of the attack (MIA\textsubscript{e} and MIA\textsubscript{i}) during sneezing in experimental group (E, \(n = 16\)) at the beginning of experiment (38 °C), after reaching the panting level (42 °C) and after recovery of BT (38 °C) as well as at corresponding time intervals (1, 2, 3) in 7 controls (C). Asterisks indicate significant differences, NS - nonsignificant differences, \(n = \) number of animals.

Fig. 7
The percentage occurrence of different types of reaction evoked by mechanical stimulation of the laryngeal area. AR - areflexia, FE - forced respiratory efforts, AP - apnoeic response in the experimental group (E) with overheating and in the control group (C).
Changes in cardiorespiratory parameters

Besides other factors, the breathing pattern is determined by body temperature. A rise in the central temperature to a certain degree or heating of the skin and mucosal thermal receptors (usually in a combination) leads to polypnoea characterized by a decrease in tidal volume (V_T), an increase in frequency of breathing and ventilation without any substantial change of blood gases and the acid-base balance. The frequency of breathing in panting is usually equal to the resonant frequency of the lungs and thoracic cage, according to the lowest work of breathing and oxygen consumption for the activity of respiratory muscles (Crawford 1962, Meyer et al. 1989) and without substantial enhancement of heat production by the work output of respiratory muscles.

In some animals, there is a biphasic response of the respiratory system to thermal stress. The primary response is characterized by an increase in breathing frequency with a decrease in V_T, secondary to a partial decline of frequency and increase in V_T when ventilation is enhanced during respiratory alkalosis (Jennings and Macklin 1972).

In our experiments, we investigated changes of some respiratory and cardiovascular parameters, blood gases, ET_CO2 and characteristics of some respiratory reflexes during hyperthermia, after reaching panting temperature level and also during cooling to the initial value of BT in rabbits. Panting has been studied mainly in dogs and only sporadic data in rabbits are available (Richards 1968, Nicol and Maskrey 1977).

We have found that the increase in BT was accompanied in all rabbits by an increase in the frequency of breathing and ventilation besides an increase in V_T. After reaching a certain body temperature (41.15 °C on the average) there was a dramatic increase in the frequency of breathing, a decrease in V_T and involvement of auxiliary respiratory muscles. The frequency of breathing during panting in our experiments was lower than in those of Nicol and Maskrey (1977) carried out in conscious New Zealand white rabbits with a frequency up to 500 x min^-1. The frequency of breathing during panting in our
experiments was probably influenced by the inhibiting effect of pentobarbital anaesthesia.

In accordance with others (e.g. Albers 1961), we found no marked change in \( \text{PaCO}_2 \) during panting. End-tidal \( \text{CO}_2 \), which was in the physiological range up to the highest body temperatures, decreased dramatically during panting and the inspiratory fraction of \( \text{CO}_2 \) was increased in 44\% of rabbits, probably as a result of the decrease in \( V_T \) and enhanced rebreathing from \( V_T \). This increased \( \text{CO}_2 \) concentration in inspired air may have a physiological compensatory effect against extreme hypocapnia.

The heart rate during elevation of BT became accelerated without any substantial change of systemic blood pressure. Besides assumed vasodilation, tachycardia was probably one of the mechanisms responsible for the enhancement of cardiac output as well as reported by Jennings et al. (1973) in conscious dogs during panting. In contrast to their results, we did not find any increase in systemic blood pressure during overheating in rabbits.

During cooling, ventilation was increased further mainly as a result of the more rapid enlargement in \( V_T \) thus affecting \( \text{ETCO}_2 \) and blood gases. Hypocapnia was intensified in this phase. These effects resemble the second phase of thermal polypnoea, with the exception that these effects accompanied the decrease in rectal temperature and in \( \text{pH} \) metabolic acidosis. Explanations of the drive for increased \( V_T \) during the recovery phase are only hypothetical (effects of some humoral substances, etc.).

The phase of recovery from hyperthermia to the initial BT was indicated by Galland et al. (1991) as a phase of impaired breathing control. These authors showed that during recovery from experimental hyperthermia in piglets the ventilatory pattern becomes extremely variable. During this phase, we also found marked changes in blood pressure – massive hypotension characterized by the decrease of blood pressure up to a half of the initial value. Hypotension probably resulted in enormous vasodilation. This seems to be the cause of sudden failure of vital functions followed by death of six rabbits. These animals were consequently excluded from the final statistical data analysis.

Changes in respiratory reflexes

The main aim of our study was to investigate changes in respiratory reflexes during thermal polypnoea. The Hering-Breuer inflation reflex was studied under these circumstances mainly in dogs by other authors. Hammouda (1933) observed that the HB reflex was diminished in anaesthetized dogs with a frequency of breathing higher than 75 per minute and it was generally absent at a respiratory rate above 120 per minute. On this basis, Hammouda defined the lower limits of panting in dogs as 120 breaths per minute. Richards (1968) found that there are differences between animal species in the importance of vagal receptors during panting. Vagotomy had only a weak effect on panting in one studied rabbit.

In our experiments on rabbits, together with an increase in frequency of breathing the duration of the inflation reflex was shortened during overheating. However, there was no significant change in the strength of this reflex. After a sudden change in the pattern of breathing – appearance of panting – the inflation reflex was a significantly decreased. It seems that the breathing pattern during panting in rabbits is subordinated to the dominant intrinsic rhythm of respiratory centers with diminished regulatory influences from pulmonary stretch receptors.

Hyperthermia due to overdressing or high environmental temperature has been implicated as a possible cause in some cases of the sudden infant death syndrome (SIDS). It may also lead to a loss of sensitivity of the respiratory chemoreceptor (Gozal et al. 1988). The loss of chemoreceptor function may be of great importance, e.g. during hypercapnia caused by rebreathing in infants sleeping facedown on soft bedding (Chiodini and Thach 1993) or in the chemoreflex ventilatory response in fever (Maskrey 1995).

The elicitability and intensity of protective and defensive respiratory reflexes are influenced by many factors. We have investigated the protective and defensive upper airways reflexes during hyperthermia. The duration and strength of apnoeic reflexes from the nose and larynx was shortened and diminished in our experiments mainly during panting. It is questionable, if these reflexes, being essentially briefer, could still protect lower airways and lungs against the penetration of noxious substances.

In contrast to our results in rabbits with upper airways apnoeic reflexes, Berterottière et al. (1990) have found that mild hyperthermia (+0.8 °C in BT) did not significantly modify the duration of central and obstructive apnoea in premature infants.

The effects of hyperthermia on coughing in cats was studied by Korpás and Tomori (1958). They found that mechanically induced cough is gradually diminished with increasing body temperature until the cough reaction ceased completely.

In our experiments even at the panting level, it was possible to elicit defensive airway reflexes in rabbits, however, with less strength and efficiency. The expulsion response was replaced by an apnoeic reaction in 76\% of laryngeal stimulation. This may serve as evidence of reduced reflex irritability manifested by replacement of a complex inspiratory-expiratory forced response by more simple reaction-inhibition of breathing – a change which can be seen in deeper stages of anaesthesia after large doses of antilittussives or in hypothermia (Korpás and Tomori 1979).
Our results show that the breathing pattern in panting is fully aimed to cover thermoregulatory and enhanced metabolic needs so that the defence of airways and lungs against the penetration of injurants is reduced. The intrinsic rhythm of the respiratory center becomes dominant with diminished reflex and chemical control of breathing during thermal polypnoea and panting in anaesthetized rabbits.

References


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