Comparison of inspiratory effort in sniff-like aspiration reflex, gasping and normal breathing in cats

Z. Tomori, V. Donič, M. Kurpas

Comparison of inspiratory effort in sniff-like aspiration reflex, gasping and normal breathing in cats. Z. Tomori, V. Donič, M. Kurpas.
ABSTRACT: The changes in airway occlusion pressure and airflow, occurring during two spasmodic breathing patterns, were studied and compared with normal breathing pattern in 12 anaesthetized cats.

The inspiratory effort developed during the sniff-like aspiration reflex elicited by mechanical stimulation of the nasopharynx under control conditions proved to be very similar in character and intensity to the activity observed during gasping which occurred on resuscitation, of the same cats, from hypoxic apnoea. The starting (P_{50}) and maximum (P_{max}) airway occlusion pressure developed in these two spasmodic breathing patterns were very high. Extremely rapid rates of contraction and relaxation were detected by computer-assisted measurements of dynamic changes in both the pressure values and the slopes of pressure curves.

The results suggest common effector mechanisms, reflecting similar forceful inspiratory drives, for the aspiration reflex and gasping. These two spasmodic processes differ substantially from normal breathing. Nevertheless, the aspiration reflex differs from gasping in that it can be elicited by activation of upper airway afferents during eupnea. Moreover, as yet, there is no definitive evidence that the brainstem mechanisms responsible for generating the aspiration reflex are the same as those of the gasp. The main benefits of this reflex are its rather easy elicitability under various conditions and its capability to induce important cardiorespiratory effects (*e.g.*) reversal of central apnoea) owing to its powerful activity.
Eur Respir J., 1993, 6, 53–59.

The apnoea caused by hypoxia or asphyxia of various origin may be reversed by spontaneous gasping, which has been referred to as autoresuscitation [1, 2]. However, for some unknown reason, recovery from apnoea by gasping may not take place in serious breathing disorders such as sudden infant death syndrome, and sleep apnoea syndrome, as well as various forms of central apnoea (3–4). Therefore, there have been efforts to study, in experimental models, both the central control mechanisms of breathing and recovery from apnoea. The effectiveness of autoresuscitation by gasping is reduced by general anaesthesia and sleep compared to the awake state, and it varies widely with age, animal species and anaesthetics used [2, 5–8]. During previous experiments in adult cats anaesthetized with sodium pentobarbitone, autoresuscitation by gasping was effective in approximately only 20% of apnoeic episodes induced by inhalation of pure nitrogen. Hypoxic apnoea could be reversed more often by repeated evocation of the sniff-like aspiration reflex [9]. This reflex can be induced by mechanical stimulation of the nasopharyngeal mucosa and comprises an extremely strong and fast inspiratory effort [10–13] resembling a gasp, and also a

sniff which is a semi-reflex response that occurs in animals when a new odour attracts attention [14]. In man, sniffing is mostly a voluntary behavioural act originating from the cortical area 6 b [15].

Fast and powerful activation of practically all phrenic motoneurons and inspiratory muscles is typical of gasping [2, 16], the aspiration reflex [10–13, 17] and sniffing [18]. Because the striking similarities of these forced inspiratory processes are obvious, we found it reasonable to compare them using a multiparametric analysis. Analysis of the breathing pattern suggested that the inspiratory airflow is practically the same in sniff-like aspiration reflex and the gasp [19]. But since the airflow rate can be limited by various mechanisms such as the actual lung volume, and respiratory resistance, airway occlusion pressure was chosen to characterize the inspiratory effort, reflecting the gradual activation and overall contraction and relaxation of the muscles recruited in the respiratory processes studied.

The aim of our study was: 1) to investigate the changes in the airway occlusion pressure developed during both periodic gasping and the aspiration reflex provoked by mechanical stimulation of the upper

airways, compared to normal breathing; 2) to analyse the dynamics of changes in pressure intensity and rates of contraction and relaxation that characterize the three respiratory patterns studied; and 3) to discuss some characteristic features of the spasmodic inspiratory efforts in gasping and the aspiration reflex compared with normal breathing. Some results have been published in an abstract form [20].

Methods

The experiments were performed in 12 adult cats (weight 1.8–3.0 kg) anaesthetized with sodium pentobarbitone (Pentobarbital Spofa 40 mg·kg^{-1}, given intraperitoneally). In order to achieve satisfactory levels of anaesthesia, supplementary doses of pentobarbitone were given, when limb movements could be elicited by pinching of the skin. A tracheal catheter was introduced to allow spontaneous breathing of room air or pure N_2 from a cylinder, or to apply artificial ventilation when needed. A wide ventrolateral pharyngostomy was performed to allow mechanical stimulation of the nasopharynx (fig. 1). An 0.3 mm diameter elastic nylon fibre was used to elicit the aspiration reflex mechanically [10, 11].

Control recording of several eupnoeic breaths and aspiration reflexes was followed by N_2 inhalation, to induce hypoxic apnoea [21]. Usually, after 40–50 s of apnoea, there was marked mydriasis, indicating the onset of brainstem paralysis, and a mandatory type of artificial ventilation with air (Bird, Mark 7) combined with cyclic compression of the chest was induced. Typical periodic gasps occurring in six out of 12 cats resuscitated from hypoxic apnoea were compared with the sniff-like aspiration reflexes and normal breaths recorded in control conditions before N_2 inhalation in the same cats.

End-tidal CO_2 monitored in part of the experiments indicated 3.5–4.0 volume % for control conditions when the normal breaths and aspiration reflexes were recorded. The periodic gasps were selected from anaesthetized cats performing autoresuscitation from hypoxic apnoea at end-tidal CO_2 values varying between 3–4 volume %. The airflow and airway occlusion pressure were continuously recorded on a thermal array polygraph. The signals were stored on magnetic tape (EAM 340, Tesla) and on-line or off-line evaluated by a microcomputer. The inspiratory efforts of normal breaths, aspiration reflexes and gasps were calculated from the changes in airway pressure developed during transient plugging of the
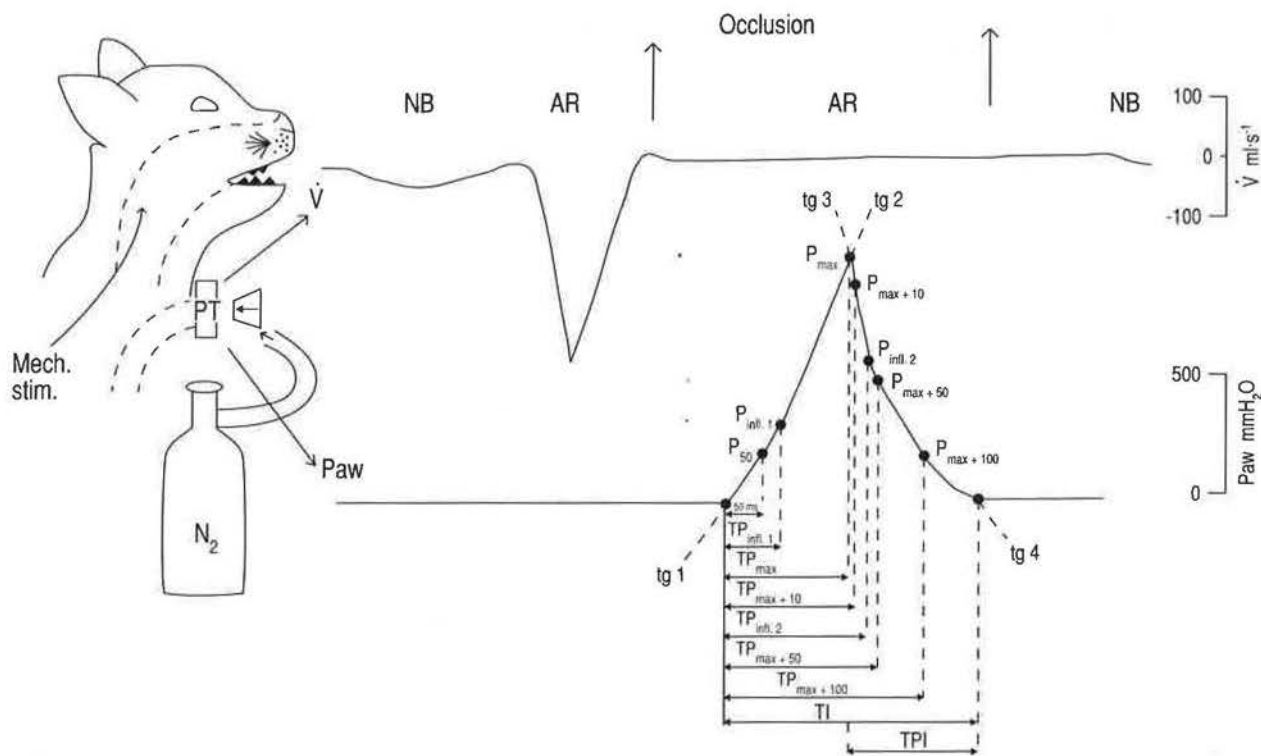

Fig. 1. – Schematic diagram of the experiments in anaesthetized cats. Induction of apnoeic episodes by nitrogen (N_2) inhalation, mechanical stimulation (mech. stim.) of the nasopharynx, parallel recording of airflow ($\dot{V}$) and airway occlusion pressure (Paw) by a pneumotachograph (PT) before, during and after plugging of the tracheal tube (occlusion), and evaluation of various parameters during normal breath (NB), aspiration reflex (AR) tg: rate of change in Paw during airway occlusion (1–4 denote 4 slopes). For details see methods. P_{50}, P_{max}, P_{max+10}, P_{max+50}, $P_{max+100}$, $P_{infl\ 1}$, $P_{infl\ 2}$: pressure intensity at 50 ms from the beginning, at maximum value, then 10, 50 and 100 ms after maximum as well as at the first and second inflection points on the ascending and descending parts of the curve, respectively. TP_{max}, TP_{max+10}, TP_{max+50}, $TP_{max+100}$, $TP_{infl\ 1}$, $TP_{infl\ 2}$: time to reach these pressure intensities; TI: time of total inspiratory period; TPI: total post inspiratory period.

tracheal tube performed for 10–15 s (fig. 1). The method of airway occlusion pressure measurement was the one that is generally used for experimental and clinical investigations.

The rate of neuromuscular recruitment and relaxation rate [22, 23] characterizing the inspiratory effort in the aspiration reflex, gasp and normal breath were evaluated according to various parameters calculated from the pattern of the airway occlusion pressure changing from zero level to strong subatmospheric values (inspiratory part) and back to zero (postinspiratory part) (fig. 1). In order to characterize the three respiratory processes in greater detail, the amplitude, time and slope were determined by the computer at typical points on the airway pressure curve. The following 19 parameters were measured: pressure intensity achieved at 50 ms from the beginning, at the maximum value, then 10, 50 and 100 ms after the maximum as well as at the first and second inflection points of the ascending and descending parts of the curve (P_{50}, P_{max}, P_{max+10}, P_{max+50}, $P_{max+100}$, $P_{infl\ 1}$, $P_{infl\ 2}$ respectively), the time to reach these intensities (TP_{max}, TP_{max+10}, TP_{max+50}, $TP_{max+100}$, $TP_{infl\ 1}$, $TP_{infl\ 2}$, respectively) and the time of both the total inspiratory and postinspiratory periods (TI and TPI respectively). The slopes of the curve before and after the first and second inflection points (tg 1, tg 2, and tg 3, tg 4) were also evaluated. The airflow was also recorded and evaluated before and after tracheal occlusion and the analysis of the breathing pattern was used for better characterization of the respiratory processes investigated.

Altogether 55 aspiration reflexes were analysed in 10 cats, together with 67 gasps from 6 animals and 38 normal breaths from 11 cats. Using these data, the mean values of the starting and maximum pressures characterizing the inspiratory effort were calculated for each animal, as well as for the three respiratory processes.

In order to study the dynamics of changes the contraction and relaxation rates of the inspiratory effort were investigated in detail in a smaller sample, since only one representative record for each process from each cat was available for technical reasons. Altogether, 10 aspiration reflexes, 6 gasps and 11 normal breaths were analysed for this purpose.

The aspiration reflex, gasp and normal breath were compared using two-sample analysis of the mean values calculated in an IBM PC AT computer for each cat (in the larger group) or their representative records available (in the detailed analysis from the smaller sample). Student's t-test for unpaired and independent samples was used. Population differences were considered significant if p was <0.05. The results of experiments are given as means and standard errors of the means (mean+SEM).

Results

The airflow and airway occlusion pressure records shown in figure 2 demonstrate that repetitive mechanical stimulation of the nasopharynx evokes
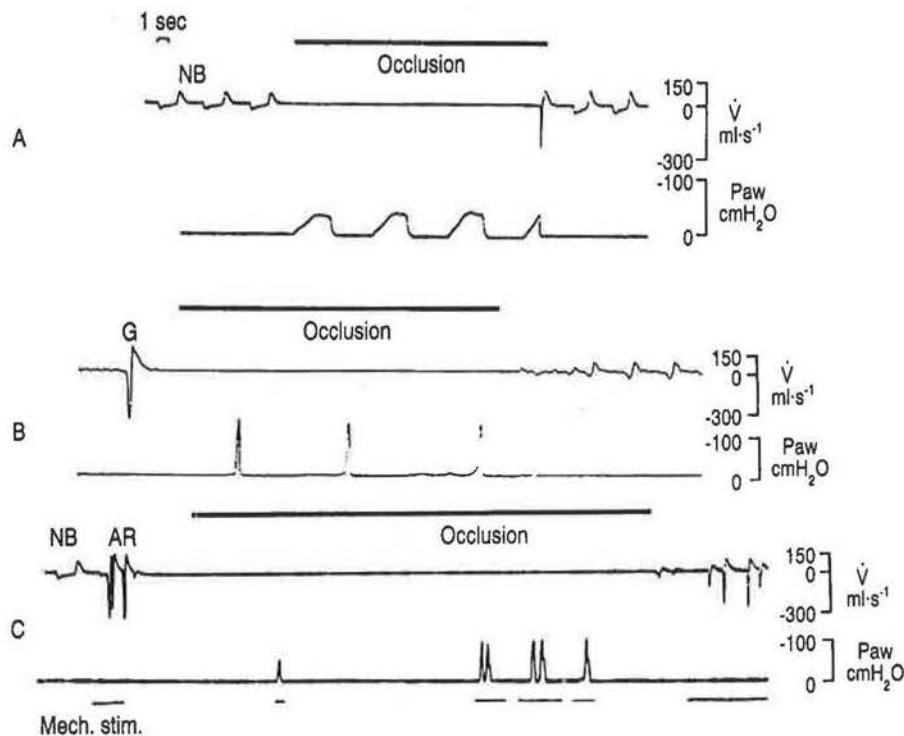

Fig. 2. – Polygraphic recording of airflow (V̇) and airway occlusion pressure (Paw) before, during and after tracheal occlusion in normal breathing (NB); periodic gasping (G); and aspiration reflex (AR) induced by mechanical stimulation. Mech. stim.: mechanical stimulation of the nasopharynx with a nylon fibre. Panels A, B and C are records from different sections of experiments in the same cat.

aspiration reflexes (AR in panel C), differing substantially from the normal breaths (NB in panel A).

The pattern of airflow and the airway occlusion pressure records during these reflexes seems to be practically the same as those in the periodic gasping occurring in the same experiment during resuscitation from hypoxic apnoea (G in panel B). However, the aspiration reflex differs substantially from gasping by co-existence of some eupnoeic breaths occurring before or after several spasmodic inspiratory reactions to nasopharyngeal stimulation (NB in panel C), as discussed later.

Table 1. – Mean values (mean±SEM) of some pressure and time parameters in the sniff-like aspiration reflex (AR) and gasp (G) compared to normal breath (NB)

		P_{50} mmH$_2$O	P_{max} mmH$_2$O	TI ms	TP$_{max}$ ms
AR n=10	mean	71*	734*	369*	125*
	±SEM	16.0	49.4	50.9	25.4
G n=6	mean	89*	772*	297*	104*
	±SEM	6.9	37.8	22.9	8.9
NB n=11	mean	5.9	127	2091	1552
	±SEM	1.2	22.1	270	231

There are no significant differences between AR and G, but they differ significantly from normal breaths. *: less than 0.01; n: number of animals. P_{50}: pressure intensity achieved at 50 ms from the beginning; P_{max}: maximum pressure; TI: total inspiratory period; TP$_{max}$: time to reach maximum pressure. See legend to Fig. 2 for further abbreviations.

Fig. 4. – Contraction and relaxation rates in various phases separated by characteristic points (P_{50}, P_{max}, etc.) in the aspiration reflex, gasp and normal breath expressed as percentage changes of airway occlusion pressure (% Δ Paw) within 10 ms, compared to maximum pressure (P_{max}) (similar to method in [23]). Significant differences: *p<0.05; **p<0.01; ***p<0.001. ☐: aspiration reflex(n=10); ▨: gasp (n=6); ▮ : normal breathing (n=11).

The original records (fig. 2) and the results summarized in table 1 and figures 3–5 indicate that inspiratory efforts developed during tracheal occlusion are very similar in the two spasmodic respiratory processes, but are markedly different from normal breaths. The data collected from a larger group (table 1) indicate that the spasmodic inspiratory efforts in aspiration reflex and gasp generate 6–15 times stronger starting and maximum values of occlusion pressure
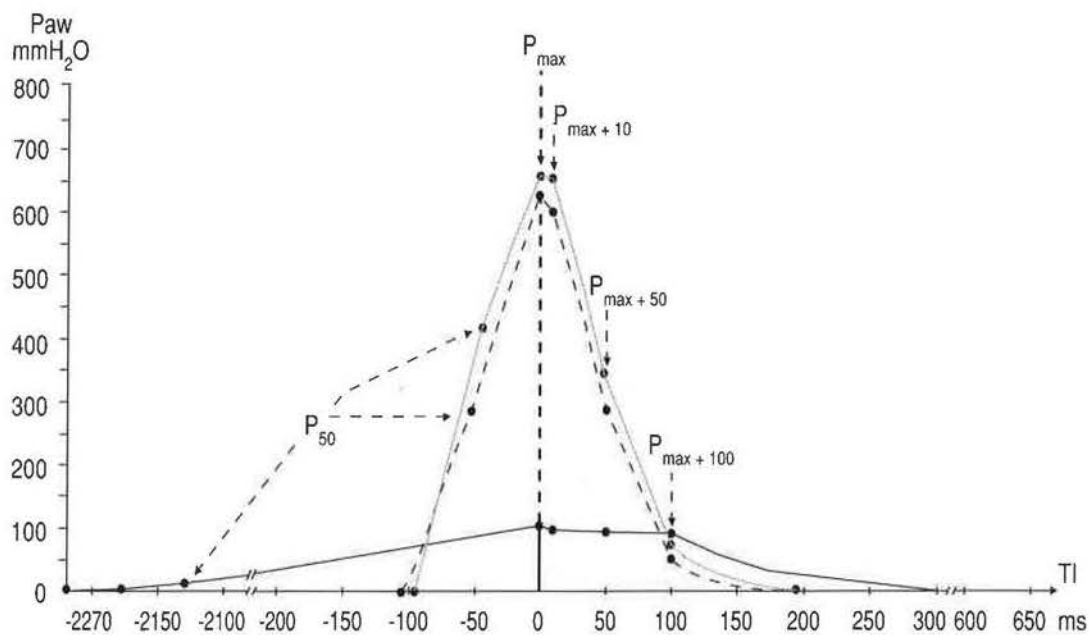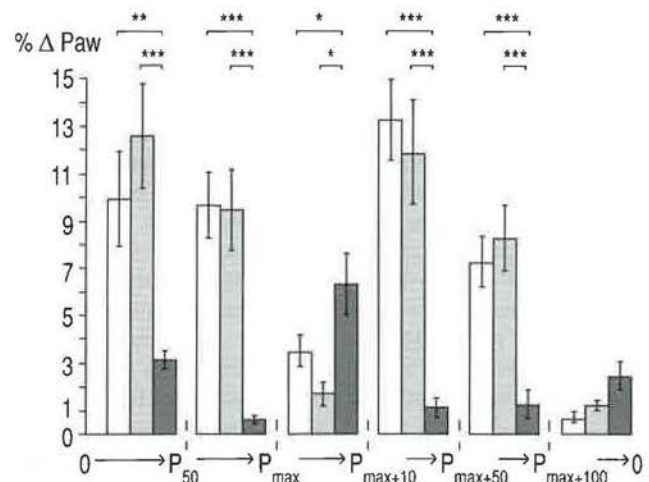

Fig. 3. – Dynamics of airway occlusion pressure changes during the gasp (G), aspiration reflex (AR) and normal breath (NB), performed during airway occlusion. The curves are constructed from the mean values of P_{50}, P_{max}, P_{max+10}, P_{max+50} and $P_{max+100}$. The patterns of the three respiratory processes are compared before and after their maximum pressures (P_{max}) superimposed at 0 value on a common scale of total inspiratory time (TI). —— : normal breath (n=11); - - - -: aspiration reflex (n=10); ········: gasp (n=6). For further abbreviations see legend to figure 1.

within a 6–15 times shorter time than in normal breaths.

From the results of detailed analysis in a smaller group, comprising one typical record from each cat, the average pattern of the airway occlusion pressure was computed to characterize the general dynamics of pressure changes in the three processes studied (fig. 3). Figure 4 indicates the airway occlusion pressure expressed in % change of maximum pressure within 10 ms, in a similar way to that used in human subjects [23]. The changes are very high in both spasmodic processes compared to normal breathing, especially during 50 ms from the beginning of inspiration ($0-P_{50}$, indicating the maximum contraction rate) and between the 10th and 50th ms from the peak values ($P_{max+10}-P_{max+50}$, expressing the maximum relaxation rate). Figure 5 indicates the slopes of the preinflection and postinflection portions of both the ascending (tg 1, tg 2) and descending parts (tg 3, tg 4) of the airway occlusion pressure curve. The slopes indicate that the rate of contraction (tg 1) as well as the relaxation rate (tg 3) are very similar in the aspiration reflex and gasp, differing rather significantly from normal breath.
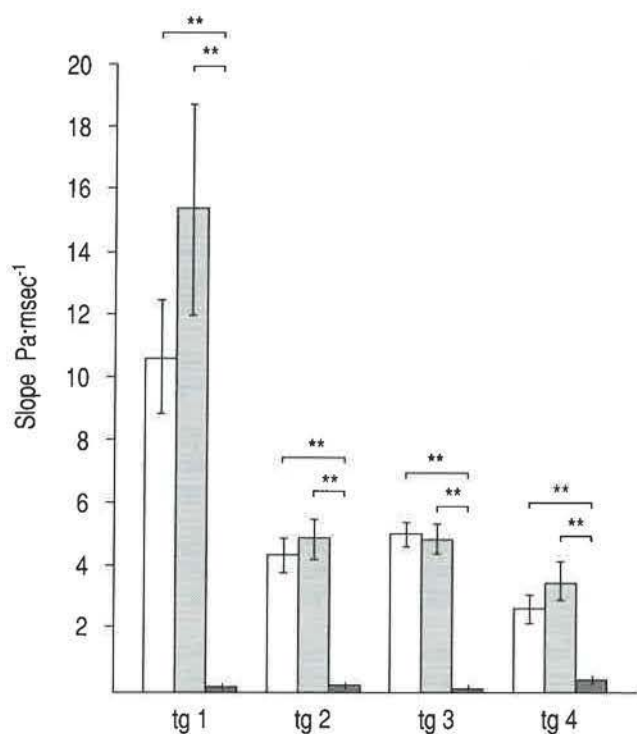

Fig. 5. – Airway pressure changes during airway occlusion expressed as slopes of both the ascending (tg 1, tg 2) and descending parts (tg 3, tg 4): preinflection (tg 1, tg 3) and postinflection portions (tg 2, tg 4) in aspiration reflex (AR), gasp and normal breath. Significant differences; ** : p<0.01. ☐:aspiration reflex (n=10); ▨ : gasp (n=6); ▮ : normal breathing (n=11).

Discussion

In anaesthetized cats, the gasp and the sniff-like aspiration reflex evoked by mechanical stimulation of the nasopharynx are very similar in some respects but different in others.

Both processes are characterized by powerful inspiratory effort resembling an all-or-nothing reaction in character, and appearing as very similar high-frequency activities in diaphragmatic electromyograph (EMG) and phrenic electronystagmograph (ENG) [2, 11, 16, 17, 24–26] and rapid and strong inspiratory airflows exceeding many times the eupnoeic breaths [2, 19]. The airway occlusion pressures (especially P_{50}, P_{max} and P_{max+50}) are also very similar in both spasmodic inspiratory processes, starting suddenly and finishing abruptly. The rate of contraction, as well as the relaxation rate expressed as percentage changes of maximum airway occlusion pressure in 10 ms (fig. 4) and as slopes of the pressure curve (fig. 5), are extremely high in both spasmodic processes, indicating the prompt involvement of neuromuscular control. The maximum relaxation rates (MRR) described during sniffing manoeuvres in human subjects [23] are of the same order as those observed in both spasmodic processes. In gasping occurring after short-term hypoxic-apnoeic episodes there was no marked effect of acute hypoxia on MRR, as has also been shown in man [27]. In addition to manual measurement of MRR [23], the computerized evaluation of both the MRR and the slopes of airway occlusion pressure changes (especially tg 1 and tg 3), successfully applied in our experiments, could also be useful for the detection of pathological alterations in respiratory muscle contraction and relaxation, *i.e.* in muscle fatigue.

The expiratory effort characterized by activity in internal intercostal and abdominal muscles is temporarily inhibited during both gasping [2, 26] and aspiration reflex [12, 13].

The same medullary inspiratory neurons may be involved in both processes, accounting for their similarities. Gasping is generated independently of eupnoeic neurogenesis through the activity of pacemaker elements localized in the lateral tegmental field, ventrolateral to the dorsal respiratory group [2]. Neurons in the areas close to the ventrolateral nucleus tractus solitarius appear to be active in spasmodic respiratory acts [18, 28, 29]. Nevertheless, different nervous inputs promoting gasping and aspiration reflex, as well as various central and peripheral actions of hypoxia inducing gasping, will result in many differences between the two spasmodic respiratory processes, as discussed later.

Both processes possess strong resuscitation efficacy frequently resulting in recovery from hypoxic or asphyxic apnoea due to rapid aeration of the lungs and strong intero- and proprioceptive inputs [2, 9, 16].

In addition to the clinically important resuscitative effects of spasmodic inspiratory efforts and other characteristics common to both processes, there are some peculiar properties and many reflex effects involved only in the aspiration reflex.

It is a reflex in origin and physiological in character. Therefore, it can also be elicited during eupnoea, and thus it is possible to alternate the reflex with eupnoeic breaths, (fig. 2C). The reflex can immediately interrupt the ongoing inspiratory-expiratory cycle

quite independently of the level of inspiratory or expiratory airflow or the instantaneous lung volume. Therefore, there is a variable lung volume at the onset of the reflex, whereas gasps always start from functional residual capacity (FRC) and zero airflow (fig. 2B). Aspiration reflexes starting from the lung volumes above FRC may develop smaller maximum occlusion pressures and, hence, smaller inspiratory efforts, as also described for the maximum sniff-generated mouth and transdiaphragmatic pressures [30].

The reflex can also be made to interrupt various kinds of apnoea in anaesthetized cats [12, 13, 21] causing a violent arousal which may contribute to a higher recovery rate from hypoxic apnoea by the aspiration reflex than by gasping [9]. Hence, investigation of the arousal effect of the airway stimulation could contribute to the explanation of some questions in the pathogenesis of sudden infant death syndrome. Various forms of upper airway stimulation have also proved to be useful in the treatment of different respiration-related acts, such as hiccough [31], obstructive sleep apnoea [32–34] and bronchoconstriction [35].

Upper airway stimulation can strongly activate the respiratory centre [12, 13, 24], especially the postinspiratory neurons, with a simultaneous inhibition of the expiratory neurons, giving rise to a two-cyclic rhythmogenesis of breathing [36]. Therefore, upper airway stimulation could be very useful for both the facilitation of resuscitation and testing of the respiratory centre reactivity in respiratory arrest, as well as for evocation of fictive aspiration in paralysed animals.

Nasopharyngeal stimulation can result in reflex vasoconstriction and transient sympathetic hyperactivity leading to transient systemic hypertension and ventricular extrasystoles even in paralysed animals [11–13] and in quadriplegic subjects [37], facilitating resuscitation.

However, the aspiration reflex was not observed in some species, *i.e.* rabbits possessing marked ability for gasping respiration [1, 2, 16].

Many characteristics of both the aspiration reflex and gasping, as well as their functional significance and possibilities of their application, are still only partially known and need further investigation.

References

1. Guntheroth WG, Kawabory Y, Breazeale D, McGough G. – Hypoxic apnoea and gasping. *J Clin Invest,* 1975; 56: 1371–1377.
2. St. John WM. – Neurogenesis, control and functional significance of gasping. *J Appl Physiol,* 1990; 68: 1305–1315.
3. Thach BT. – Sleep apnea in infancy and childhood. *Med Clin North Am,* 1986; 69: 1289–1315.
4. Milerad J. – Apnea of infancy. Kongl. Karolinska Medicochirurgiska Institutet, Stockholm, 1987; p124.
5. Adolph EF. – Regulations during survival without oxygen in infant mammals. *Respir Physiol,* 1969; 7: 356–368.
6. Phillipson EA, Bowles G. – Control of breathing during sleep. *In:* Cherniak NS, Widdicombe JG. eds. Handbook of Physiology. Section 3. The respiratory system. Vol. II. Control of breathing. Part 2. Bethesda Am Physiol Soc, 1986; pp. 41–48.
7. Jacobi MS, Thach BT. – Effects of maturation on spontaneous recovery from hypoxic apnoea by gasping. *J Appl Physiol,* 1983; 66: 2384–2390.
8. Jacobi MS, Gershan WM, Thach BT. – Mechanisms of failure of recovery from hypoxic apnea by gasping in 17 to 23 day-old mice. *J Appl Physiol,* 1991; 71: 1098–1105.
9. Tomori Z, Benacka R, Donic V, Tkáčová R. – Reversal of hypoxic apnea by aspiration reflex in anaesthetized cats. *Eur Respir J,* 1991; 4: 1117–1125.
10. Tomori Z. – Pleural, tracheal and abdominal pressure variations in defensive and pathologic reflexes of the respiratory tract. *Physiol Bohemoslov,* 1965; 14: 84–95.
11. Tomori Z, Widdicombe JG. – Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. *J Physiol (Lond),* 1969; 200: 25–49.
12. Korpás J, Tomori Z. – Cough and other respiratory reflexes. Basel, Munchen, Paris, London, New York, Sydney, Karger, 1979; p356.
13. Tomori Z, Javorka K, Stránsky A, Jakus J. – The pathophysiological role of the sniff-like aspiration reflex. *In:* Hutas I, Debreczeni L. eds. Advances in Physiol Sci, Vol. 10. Respiration. Medicina, Budapest, 1981; pp. 495–506.
14. Ganong WF. – Review of medical physiology. Los Altos, Lange Med Publications, 1979; p620.
15. Simpson JA, Fitch W. – Applied neurophysiology. London, Boston, Wright, 1988; p358.
16. Macefield G, Nail B. – Inspiratory augmentation during asphyxic hyperpnoea and gasping: proprioceptive influences. *Respir Physiol,* 1986; 64: 57–68.
17. Jodkowski JS, Guthrie RD, Cameron WE. – The activity pattern of phrenic motoneurons during the aspiration reflex: an intracellular study. *Brain Res,* 1989; 505: 187–194.
18. Batsel HL, Lines AJ. – Bulbar respiratory neurons participating in the sniff reflex in the cat. *Exp Neurol,* 1973; 39: 469–481.
19. Donič V, Tomori Z, Benacka R. – Characteristics of forced respiratory acts using computerized analysis of pneumotachographic records. IUPS regional meeting, Prague 1991; Abstract PE 22.
20. Tomori Z, Donič V, Benacka R, Kurpas M. – Comparison of inspiratory effort in gasping (G) and sniff-like aspiration reflex (AR) in cats. *Eur Respir J,* 1991; 4 (Suppl. 14): 249–250.
21. Tomori Z, Benacka R, Donic V, Tkácová R. – Hypoxic apnoea induced by N_2 inhalation can be reversed by the aspiration reflex in anaesthetized cats. *Respir Med,* 1991; 85 (Suppl. A): 61–65.
22. Thach BT, Schefft GL, Pickeus DL, Aravindaksha PM. – Influence of upper airway negative pressure reflex on response to airway occlusion in sleeping infants. *J Appl Physiol.* 1989; 67: 749–755.
23. Koulouris N, Vianna LG, Mulvey DA, Green M, Maxham Y. – Maximal relaxation rates of esophageal, nose, and mouth pressures during a sniff reflect inspiratory muscle fatigue. *Am Rev Respir Dis,* 1989; 139: 1213–1217.
24. Nail BS, Sterling GM, Widdicombe JG. – Patterns of spontaneous and reflexly-induced activity in phrenic and intercostal motoneurons. *Exp Brain Res,* 1972; 15: 318–332.
25. Benacka R, Tomori Z, Donič V. – Myographic

analysis of spontaneous and artificially-induced breathing patterns during anoxia in cats. *IUPS regional meeting, Prague* 1991; Abstract PE 21.

26. St'John WM, Knuth KV. – A characterization of the respiratory gasping. *J Appl Physiol: Resperiat Environ Exercise Physiol*, 1981; 50: 984–993.

27. Vianna LG, Koulouris N, Green M, Maxham Y. – Effect of acute hypoxia and hypercapnia on maximum relaxation rate of skeletal muscle in man. *Am Rev Respir Dis*, 1988; 137 (Suppl. A73).

28. Borison HL. – Electrical stimulation of the neural mechanism regulating spasmodic respiratory acts. *Am J Physiol*, 1948; 154: 55–62.

29. Jakuš J, Tomori Z, Bošel'ová L', Nagyová B, Kubinec V. – Respiration and airway reflexes after transversal brain stem lesion in cats. *Physiol Bohemoslov*, 1987; 36: 329–340.

30. Wanke T, Schenz G, Zwick H. – Dependence of maximal sniff-generated mouth and transdiaphragmatic pressures on lung volume. *Thorax*, 1990; 45: 352–355.

31. Salem MR, Baraka A, Rattenborg CC, Holaday DA. – Treatment of hiccups by pharyngeal stimulation in anaesthetized and conscious subjects. *J Am Med Assoc*, 1967; 202: 32–36.

32. Mathew OP, Remmers JE. – Respiratory function of the upper airway. *In*: Sanders NA, Sullivan CE. eds. Sleep and breathing. New York, Dekker, 1984; pp. 163–200.

33. Sullivan CE, Grunstein RR, Marrone O, Berthon-Jones M. – Sleep apnea - Pathophysiology: upper airway and control of breathing. *In*: Guilleminault Ch, Partinen M, eds. Obstructive sleep apnea syndrome: clinical research and treatment. New York, Raven press, 1990; pp. 49–69.

34. Widdicombe JG, Davies A. – The effects of a mixture of surface-active agents (Sonarex) on upper airway resistances and snoring in anaesthetized dogs. *Eur Respir J*, 1988; 1: 779–784.

35. Shturman-Ellstein R, Zeballos RJ, Buckley JM, Souhrada JF. – The beneficial effects of nasal breathing on exercise-induced bronchoconstriction. *Am Rev Respir Dis*, 1978; 118: 65–73.

36. Lawson EE, Richter DW, Czyzyk-Krzeska MF, Bischoff A, Rudesill RC. – Respiratory neuronal activity during apnea and other breathing patterns induced by laryngeal stimulation. *J Appl Physiol*, 1991; 70: 2742–2749.

37. Prys-Roberts C, Greeve LT, Maloche R, Foex P. – Studies of anaesthesia in relation to hypertension. *Br J Anaesth*, 1971; 43: 531.