PHYSIOLOGY

Mechanisms of Apnea in Cats with Labored Breathing

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Knowledge of how the respiratory system responds to the resistance which respiratory muscles overcome during pulmonary ventilation is of special significance for the physiology and pathology of respiration. An increase in the inelastic component of this resistance as a consequence of airway obstruction may be the cause of sudden respiratory arrest in patients during an exacerbation of chronic lung disease [6], in obese elderly persons during sleep, and in cases of the so-called sudden infant death syndrome [1,3]. In particular, the reduced bronchial patency responsible for prolonged and dangerous apneic episodes during REM sleep has been associated with a weakening of efferent impulse traffic from the respiratory center and a diminished tonus of the laryngeal and pharyngeal muscles [4,5]. Impaired central regulation of respiration is also the major cause of respiratory arrest in persons poisoned with a narcotic substance, in subjects whose upper airways are very strongly irritated, and in the case of progressive hypoxia [2]. Respiratory arrest, however, may also be associated with unfavorable processes occurring in the peripheral part of the neuromuscular respiratory system. It has been suggested that sudden respiratory arrests in patients with obstructive lung disease may be due to fatigue of the respiratory muscles [6].

The purpose of the present study was to elucidate the relationship between the central and peripheral mechanisms that lead to respiratory arrest in animals whose respiratory system is subjected to a prolonged and increasing mechanical load.

MATERIALS AND METHODS

In the 20 Nembutal-anesthetized cats (40 mg/kg) used in this study, inspiratory (resistive) loading was imposed by having them breathe through a narrow opening in a perforated plate. The magnitude of loading, assessed by measuring the transdiaphragmatic pressure (P_{di}) developed during the first loaded inspiration, constituted 60, 70, or 80% of the maximal transdiaphragmatic pressure ($P_{di}max$) recorded at the moment of complete airway obstruction. The transdiaphragmatic pressure and its components - esophageal and gastric pressures by which the force of respiratory muscle contractions was judged - were measured with a differential electromanometer and recorded in a loop oscillograph. Minute expiratory volume (V_E) was determined with a Krogh spirograph so modified as to make it a semiautomatic system. The total electrical activity of the phrenic nerve and

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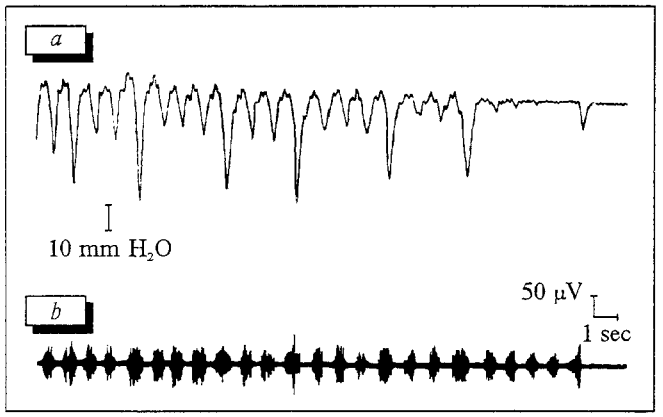

Fig. 1. Time course of transdiaphragmatic pressure P_{di} (*a*) and diaphragmatic electromyograms (*b*) taken at 30 sec before respiratory arrest in hypoxic cats during inspiratory loading.

diaphragm was recorded through platinum electrodes. Tape-recorded amplified signals were rectified and delivered to the input of an integrating R-C circuit with a time constant of 50 msec. The electrograms obtained were evaluated quantitatively by the peak values of their integrated activity. During the tests, each of which lasted 40-60 min, the cats breathed air or a hypoxic gaseous mixture (10% O_2 in nitrogen). The time courses of the O_2 and CO_2 partial pressures in alveolar gas (P_{AO2} and P_{ACO2}) were evaluated by determining the composition of the final portion of exhaled air with a mass spectrometer. Correlation/regression analysis was used for statistical processing of the data.

RESULTS

Among the cats exposed to additional respiratory loads while breathing air, a gradual fall in transdiaphragmatic pressure and the associated progressive hypoventilation were only observed in animals exposed to the heavy inspiratory load constituting 80% of the P_{di}max. Pulmonary ventilation then decreased from its baseline value of 498±36 ml/min to 219±31 ml/min by minute 30 of exposure and to 184±31 ml/min by minute 60; the transdiaphragmatic pressure dropped 23% relative to its maximal value recorded at minute 10 of exposure. Statistical treatment of the data revealed a highly significant negative correlation of P_{di} and V_E with the duration of exposure to the heavy load (r=-0.37 and r=-0.42, respectively; p<0.01). The development of alveolar hypoventilation was accompanied by progressively increasing hypercapnia and hypoxemia: by minute 60, P_{ACO2} had reached 77±11 mm Hg while P_{AO2} had fallen to 50±6 mm Hg. However, respiratory arrest did not occur and, moreover, the parameters studied all returned to their baseline values 20 to 30 min after the inspiratory loading was discontinued.

In the cats breathing the hypoxic mixture, reductions in the force of diaphragmatic contractions and the consequent decreases in pulmonary ventilation occurred even under the moderate inspiratory load (70% of P_{di}max). In such cats, the partial pressure of CO_2 in alveolar air did not exceed 40 mm Hg and that of O_2 fell to 30±3 mm Hg. Increasing the inspiratory load to 80% of P_{di}max led to respiratory arrest after 10-15 min.

Thus, respiratory arrest ensued only when the additional resistance to respiration was combined with hypoxia. Similar data have been obtained by a group of American investigators in experiments on dogs: among dogs exposed to additional inspiratory loads, apnea was observed only in those with pronounced arterial hypoxemia, and did not occur in any of the unexposed dogs with the same degree of hypoxemia. In our tests, the P_{AO2} value at which apnea set in ranged rather widely from 39.9 to 17.8 mm Hg in different cats. The time of its onset probably depended on the individual resistance of animals to hypoxia or perhaps was determined by other factors not directly associated with the contractility of the respiratory muscles.

In evaluating the state of the respiratory musculature in our test animals, it should be noted that the electrical activity of their diaphragms remained high until the complete cessation of breathing. However, 30 to 60 sec before respiratory arrest, when the electromyographic signal was at a high level, there was a progressive drop of the

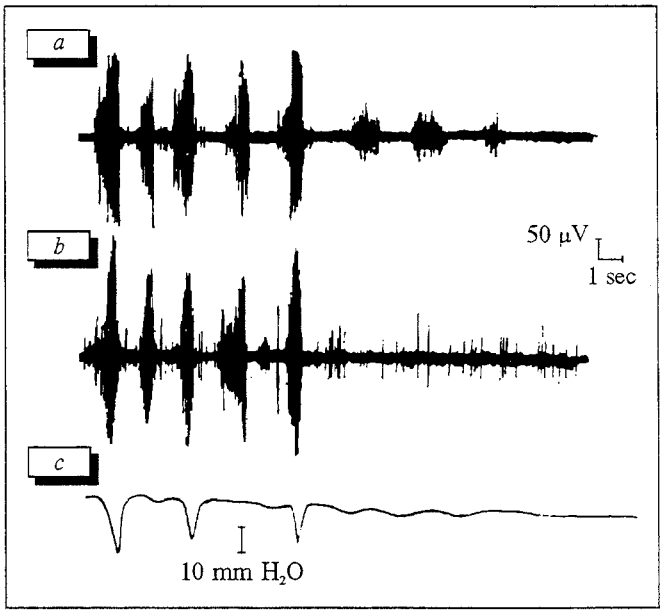

Fig. 2. Electrical activity of the phrenic nerve (*a*) and the diaphragm (*b*) recorded simultaneously with gastric pressure (*c*) in cats with respiratory arrest.

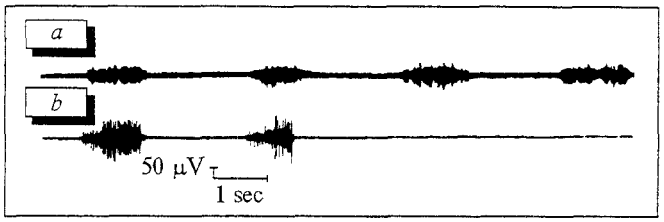

Fig. 3. Electrical activity of the phrenic nerve (*a*) and the diaphragm (*b*) at the moment of respiratory arrest.

transdiaphragmatic pressure - the principal indicator of the force with which the diaphragm contracts (Fig. 1). Moreover, just before the cessation of respiratory movements, not all bursts of diaphragmatic electrical activity were accompanied by an increase in gastric pressure (Fig. 1 and the 2nd and 4th respiratory cycles in Fig. 2). These findings are indicative of an impaired relationship between the processes of excitation and contraction in muscle fibers of the diaphragm. The diminished diaphragmatic contractility could be due to a drop of the intracellular pH because of hypoxemia and the consequent slowing of Ca^{2+} release from the sarcoplasmic reticulum, resulting in diminished interaction between the actin and myosin filaments and hence in diminished contractility of the muscle fibers.

Immediately after the respiratory arrest, when variations of the diaphragmatic pressure and its components were no longer recordable, electrical activity of the diaphragm either disappeared or changed from a phasic to a tonic variety, consisting of solitary discharges by individual motor units. Yet the electrical activity of the phrenic nerve remained phasic: several volleys of burst activity were recorded (Figs. 2 and 3). Factors determining the time of respiratory arrest appear to have included not only the reduced contractility of muscle fibers but also impaired transmission of excitation from nerve to muscle, possibly because the excitability of the muscle fiber membranes was low.

The results of this study permit the conclusion that one mechanism by which respiratory arrest occurs during exposure to an inspiratory resistive load under hypoxic conditions is the development of functional insufficiency in the respiratory muscles. However, the demonstrated peripheral nature of apnea emergence does not rule out the possibility that the central regulation of respiration is also impaired under such conditions. Interactions between the central and peripheral mechanisms that lead to respiratory arrest during functional loads and also in certain diseases are very complex and require further research using novel methodological approaches and various pharmacological agents to analyze the intimate mechanisms of this phenomenon, particularly with a view to finding methods for drug correction of the responsible respiratory disorders.

REFERENCES

1. A. M. Vein, A. V. Karlov, and M. S. Murtazaev, *Sov. Med.*, № 11, 25-27 (1988).
2. V. A. Voinov, *Central Regulation of Respiration: Neurophysiological Mechanisms Responsible for Its Impairment (Author's synopsis of doctoral dissertation)* [in Russian], Moscow (1987).
3. F. A. Abren e Sieva, U. M. MacFadden, S. A. Williams, and H. Simpson, *Proc. Roy. Soc. Med.*, **78**, № 12, 1005-1017 (1985).
4. J. Oren, in: *Physiology of Sleep*, Academic Press (1980), pp. 273-313.
5. J. E. Renmers, M. S. de Groot, E. K. Sanerland, and A. M. Anch, *J. Appl. Physiol.*, **44**, 931-938 (1978).
6. J. Yanos, M. F. Keamy, L. Leisk, *et al.*, *Amer. Rev. Resp. Dis.*, **141**, 933-937 (1990).