possible evidence that the effect of angiotensin II on cortical unit activity may be mediated to some degree through central neurotransmitter systems, cholinergic in particular.

The results are evidence that at the central neuron level, marked functional interaction of angiotensin II and bradykinin with the neurotransmitters acetylcholine and noradrenalin takes place, and it is characterized by the fact that the neuropeptides mainly potentiate and prolong the responses of the neurons to these mediators. This effect can be explained, in particular, by data showing that microinjections of angiotensin II into the cat cerebral cortex lead to increased release of acetylcholine from nerve endings, but without any effect on acetylcholinesterase activity [4]. It has also been shown that angiotensin II stimulates noradrenalin secretion by nerve endings and inhibits its reuptake [11]. It can be tentatively suggested that angiotensin II not only has a direct specific effect on cortical unit activity, mediated by heterogeneous receptors [9], but it also acts on adrenergic and cholinergic brain structures and increases neurotransmitter release from nerve endings which, in turn, excite or inhibit activity of target cells. This is confirmed, in particular, by our own experiments and data obtained by other workers who studied neurons of the preoptic region [5]. There is also evidence in the literature on the molecular effect of bradykinin on various neurotransmitter processes in certain brain structures [6, 10]. It seems likely that endogenous neuropeptides angiotensin II and bradykinin may be synaptic polymediator neuromodulators at the central neuron level.

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# REGULATION OF HUMAN RESPIRATION UNDER EXCESSIVE INTRAPULMONARY PRESSURE


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Respiration under excessive intrapulmonary pressure (EIPP) is used in clinical practice to present the development of pulmonary atelectasis, to improve gas exchange in the lungs, to reduce the strain on the inspiratory muscles [4, 15], and also in aviation medicine to maintain the pilot's oxygen supply at high altitudes [1, 2]. However, under these circumstances EIPP induces a number of unfavorable responses, mainly affecting respiration and the circulation, which limit the usefulness of this method. In particular, EIPP creates increased resistance to expiration, which has effects similar to those of the elastic resistance to respiration [12]. The fundamental physiological mechanisms of the action of EIPP on the respiratory system have been studied mainly in experiments on anesthetized animals [5, 7]. The predominant role of reflexes from the lung mechanoreceptors in the formation of the response of respiration to the action of EIPP has been demonstrated. Meanwhile the mechanisms of regulation of respiration in the conscious subject have been inadequately studied.


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TABLE 1. Changes in Basic Parameters of the Respiratory Pattern under the Influence of EIPP (40 mm Hg) without Compensation and with Optimal Counterpressure ($M \pm m$, $n = 22$)

| Parameter of respiration | Background | EIPP | EIPP + optimal compensation |
|---|---|---|---|
| $V_T$ (tidal volume), liters | 0,61±0,04 | 1,41±0,41* | 0,87±0,05* |
| $\dot{V}_E$ (minute ventilation), liters/min | 9,5±0,6 | 25,7±2,0* | 17,5±0,9* |
| $T_I$ (duration of inspiration), sec | 1,4±0,1 | 1,6±0,1 | 1,4±0,1 |
| $T_E$ (duration of expiration), sec | 2,5±0,1 | 1,6±0,1* | 1,6±0,1* |
| f (respiration rate), $min^{-1}$ | 15,4±0,4 | 18,9±1,2* | 20,1±1,3* |
| $\dot{V}_{I,peak}$ (peak inflow rate), liters/sec | 0,59±0,02 | 1,58±0,13* | 0,93±0,08* |

Legend. *$P \leq 0.05$ compared with background.

The study of the specific aspects of the regulation of respiration in man during EIPP was the main aim of the present investigation. The criterion used to reflect the dynamics of activity of the central respiratory mechanism was the electrical activity of the respiratory muscles.

## EXPERIMENTAL METHOD

Experiments were carried out on six healthy young men. Before the investigation, the subject wore a special suit with airtight helmet to create a compensating counterpressure. EIPP was created by introducing compressed gas beneath the breathing mask and it was controlled by a special reducing valve. Each session of the investigation included breathing air freely for 5 min, followed by EIPP for 2 min (40 mm Hg). In a separate series of investigations, against the background of respiration under the same pressure, a compensating counterpressure was created on the trunk on account of a controlled supply of compressed gas in the suit. The subject was instructed to be guided by his own sensations and to determine the optimal counterpressure. This procedure was repeated twice with an interval of 10 min. To record the volume-time parameters of the respiratory cycle a pneumotachographic method was used. Electrical activity of the inspiratory and expiratory muscles (the parasternal, intercostal, and external oblique muscles) was recorded by means of percutaneous electrodes. The corresponding amplification factor was provided by means of UBP 1-02 bioamplifiers. Inspiratory and expiratory activity of the muscles was estimated quantitatively according to the peak value of the envelope of the electromyogram (EMG).

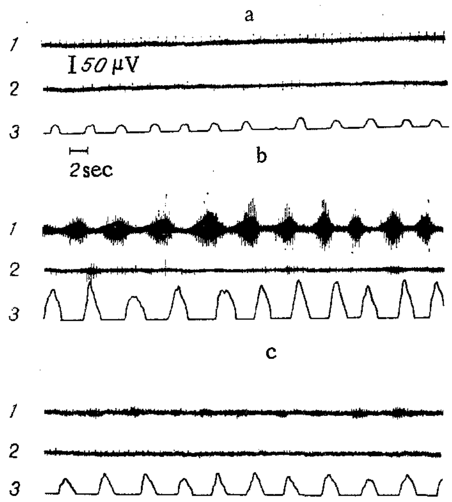


Fig. 1. Electrical activity of expiratory and inspiratory muscles during quiet breathing, breathing under EIPP without compensatory counterpressure, and with the use of optimal counterpressure. 1) EMG of expiratory muscle; 2) EMG of inspiratory muscle; 3) pneumotachogram; a) breathing air under atmospheric pressure; b) EIPP (40 mm Hg), uncompensated; c) EIPP (40 mm Hg) with optimal counterpressure.

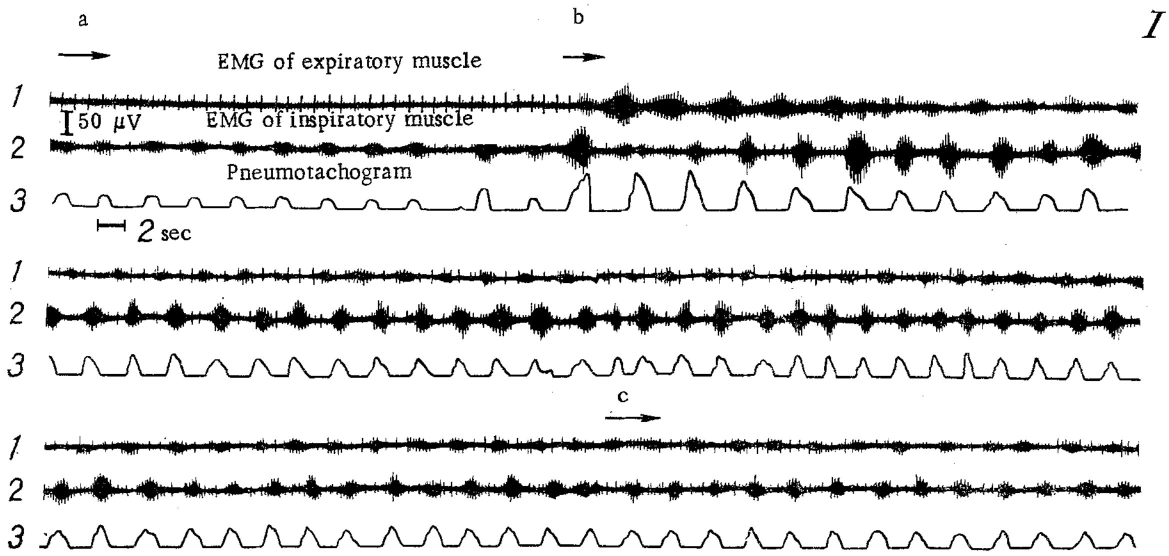


Fig. 2. Continuous recording of electrical activity of expiratory and inspiratory muscles during the search for optimal counterpressure: I) first presentation; II) second presentation in one experiment with interval of 10 min; a) breathing air under atmospheric pressure; b) EIPP (40 mm Hg) with search for optimal counterpressure; c) EIPP (40 mm Hg) with optimal counterpressure. Remainder of legend as to Fig. 1.

## EXPERIMENTAL RESULTS

Respiration under EIPP was accompanied by significant disturbances of the structure of the respiratory cycle. The most characteristic feature was hyperventilation due to an increase in the depth of respiration and its rate on account of shortening of the expiratory phase (Table 1). These facts do not agree in many respects with the results of experiments on animals. In conscious and, in particular, in anesthetized cats exposed to an EIPP of similar magnitude to that which we used (30 mm Hg), Safonov et al. [5, 6] observed marked apnea and cessation of rhythmic activity of the phrenic nerve, after which regular breathing was gradually restored, but it was slower and deeper than usual. Incidentally, after vagotomy EIPP no longer caused apnea, evidence of the reflex nature of the change in the character of respiration under EIPP: stimulation of the stretch receptors of the lungs and strengthening of inhibition of activity of the inspiratory neurons in this way (the Hering–Breuer reflex). Responses to EIPP which we found in man were not similar to the effect of stimulation of stretch receptors. They resembled more closely responses to increased elastic resistance, in which, as in the present investigation, an increase in the respiration rate and shortening of the expiratory phase were observed in addition to increased inspiratory activity [11, 13]. It can be tentatively suggested that the conscious subject responds, not so much at the bulbospinal level, as in experiments with inflation of the lungs in animals (especially if anesthetized), as (to a large extent) under influences from the cerebral cortex. This view is supported by the considerably individual differences found in the character of human breathing during EIPP [3, 9], and also the fact established previously by several investigators, and confirmed by ourselves, that responses of respiration become weaker during frequent repetition of exposures of this kind [1, 2]. Comparison of responses of the conscious and anesthetized subject to constriction of the chest leads to a similar conclusion: Under these circumstances the elastic resistance also is increased [12]. Under anesthesia a reduction of the tidal volume and in activity of the inspiratory muscles was observed with an increase in the magnitude of EIPP.

Analysis of the EMG (Fig. 1) showed a sharp increase in activity of the expiratory muscles, evidence of the appearance of active expiration under EIPP [8]. This is quite understandable, because it is resistance to expiration which increases. However, the activity of the expiratory muscles which we observed was strictly phasic, i.e., it did not extend outside expiration, and not tonic, as was noted in most published reports [5, 14]. Furthermore, according to our data, activity not only of expiratory, but also of inspiratory muscles was increased under EIPP conditions. We may recall for comparison that in anesthetized animals (cats) at the time of application of EIPP, the phasic activity of the entire respiratory musculature disappears, but later the inspiratory muscles become active not only in inspiration, but also in expiration [5]. According to other data, activity of the inspiratory muscles falls steadily in animals during exposure to EIPP [8]. It can be postulated that the role of increased activity of the inspiratory muscles is to maintain the transdiaphragmatic pressure gradient essential for maintaining the venous return to the heart [10]. In our opinion, in the conscious subject increased inspiratory activity during EIPP is largely under voluntary control, and resembles in character the "yielding negative" work in cyclic locomotions, and under those conditions it protects the lungs against overstretching.

Analysis of breathing under EIPP combined with optimal counterpressure showed that electrical activity of the inspiratory and expiratory muscles comes to resemble the background pattern (Fig. 1). Meanwhile changes in the volume-time parameters of the respiratory cycle remained considerable relative to the background values (Table 1). The subject experiences a sensation of maximal comfort while breathing under EIPP with, evidently, the smallest strain on the respiratory muscles, and for that reason he first attempts to reduce the work of the respiratory muscles, doing this voluntarily. The above remarks are confirmed by the fact that during repeated choice by the subject of optimal counterpressure, his searching time was appreciably shortened (Fig. 2), i.e., we are dealing with the formation of a temporary connection of the after-memory type.

The results show that in the conscious subject reflex influences from mechanoreceptors of the lungs do not play a determinant role in the regulation of respiration under EIPP, and that mechanisms at the suprabulbar level are pre-eminent.

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