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Respiratory and Circulatory Disorders in Experimental Poisoning with an Organophosphorus Pesticide

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Acute poisoning with Anthio is associated with a gradual drop of blood pressure in the greater circulation and the development of intensive metabolic acidosis, despite normoxia still observed in the arterial blood and a somewhat increased oxygen capacity of the blood, this indicating mitochondrial injury and disordered tissue respiration.

Key Words: *acute poisoning; organophosphorus compounds; respiration; circulation; cat*

The wide use of chemicals in agriculture, household use of toxic chemicals, and the emergence of toxicomania present a whole array of practical medical problems such as rapid diagnosis, effective treatment, and prevention of possible complications in subjects suffering from acute and chronic poisoning. Pesticides of the group of organophosphorus compounds (OPC) are priority objects to be studied because of their high toxicity and chemical stability. Accumulating in the soil, water, and foodstuffs, they may lead to imperceptible chronic poisoning of the population and, in the case of large-scale uncontrolled consumption, to acute poisoning, this frequently resulting in unpredictable complications and grave consequences. Reports have been published on a relationship between the intensity of pesticide use in agricultural regions and the incidence of respiratory diseases in the local population [1,2,5,7].

The aim of this research was a comprehensive examination of the activities of the respiratory, cardiovascular, and circulatory systems in anesthetized cats exposed under conditions of an acute experiment to the agent Anthio (formothion, Sandoz), an OPC systemic insecticide and acaricide widely used in agriculture to protect plants from pests.

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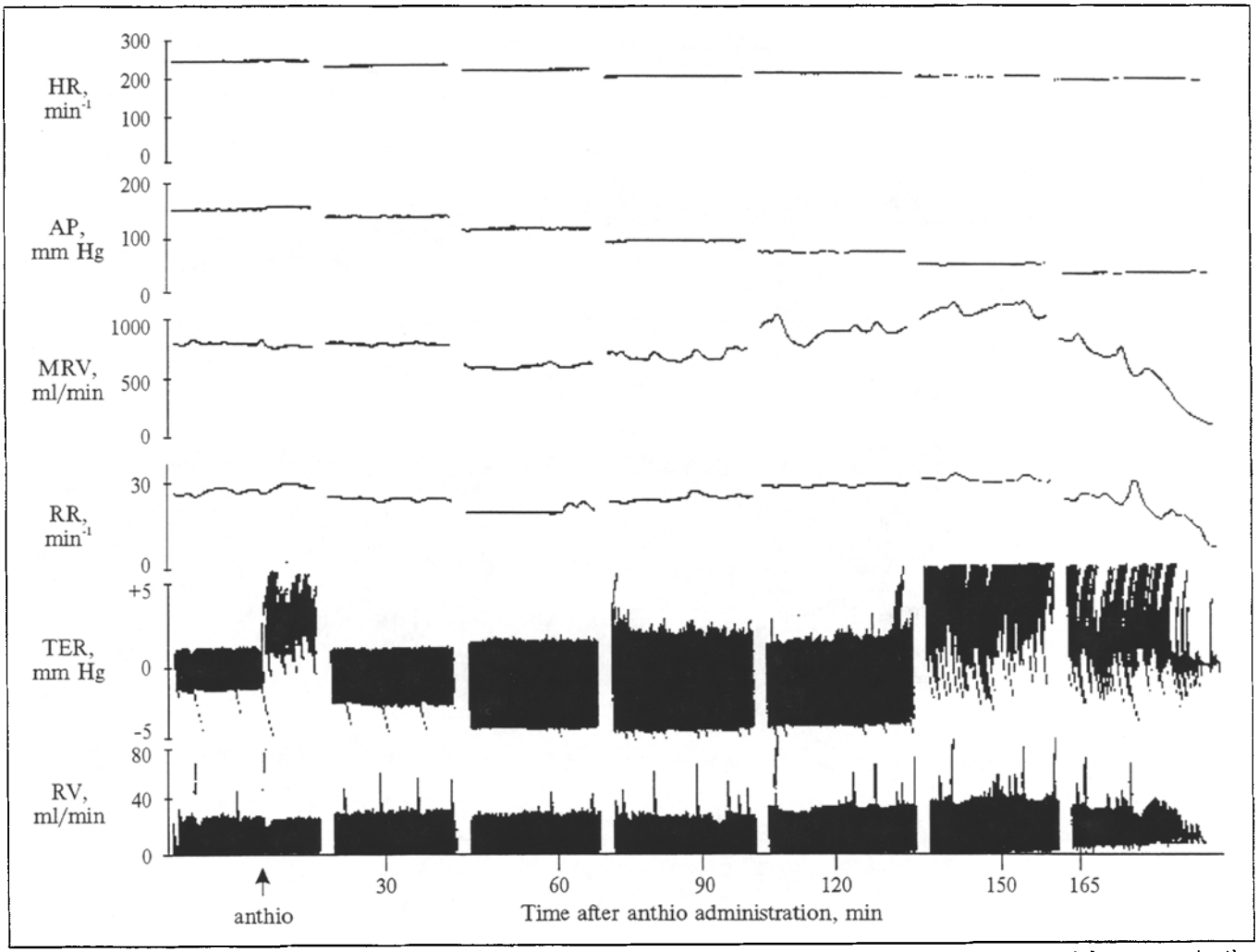

Fig. 1. Effect of Anthio on hemodynamics and ventilation of the lungs in narcotized cats. *AP*: mean arterial pressure in the greater circulation.

MATERIALS AND METHODS

Experiments were carried out with outbred cats of both sexes weighing 1.75 to 3.6 kg narcotized with nembutal, 40 mg/kg intraperitoneally. Formathion emulsion was administered to the stomach through a tube in a dose of 20% of LD_{50}, the total volume, together with the drainage fluid, not exceed-

TABLE 1. External Respiration Parameters in Narcotized Cats after Administration of Anthio (mean±SEM; $n = 13$)

Parameter	Time, min							
	0	30	60	90	120	150	180	210
MRV, ml/min	773±95	836±118	857±147	747±93	1020±217	912±164	1110±302	775±118
RR, cycles/min	27.0±2.1	26.3±2.0	27.5±2.7	28.4±3.2	28.4±3.2	28.3±3.5	28.6±3.9	25.3±5.6
RV, ml	23.8±1.6	27.0±2.1	27.2±2.6	27.5±2.6	28.9±2.8	30.4±3.6	33.8±4.2*	32.7±8.8
Maximal inhalation rate, liters/min	4.4±0.5	6.3±0.8	8.3±1.1*	8.4±0.7*	10.2±1.2*	9.3±1.7*	8.6±1.7*	8.3±2.3
Maximal expiration rate, liters/min	4.7±0.5	4.3±0.4	4.9±0.4	4.5±0.4	5.3±1.0	4.4±0.4	5.6±1.0	5.8±0.9
TEP amplitude, mm Hg	6.2±0.5	7.8±1.5	11.8±2.4*	12.9±1.7*	12.1±1.1*	12.5±2.0*	11.8±0.3*	–

Note. Here and in Tables 2 and 3: asterisk shows reliability of differences ($p<0.05$).

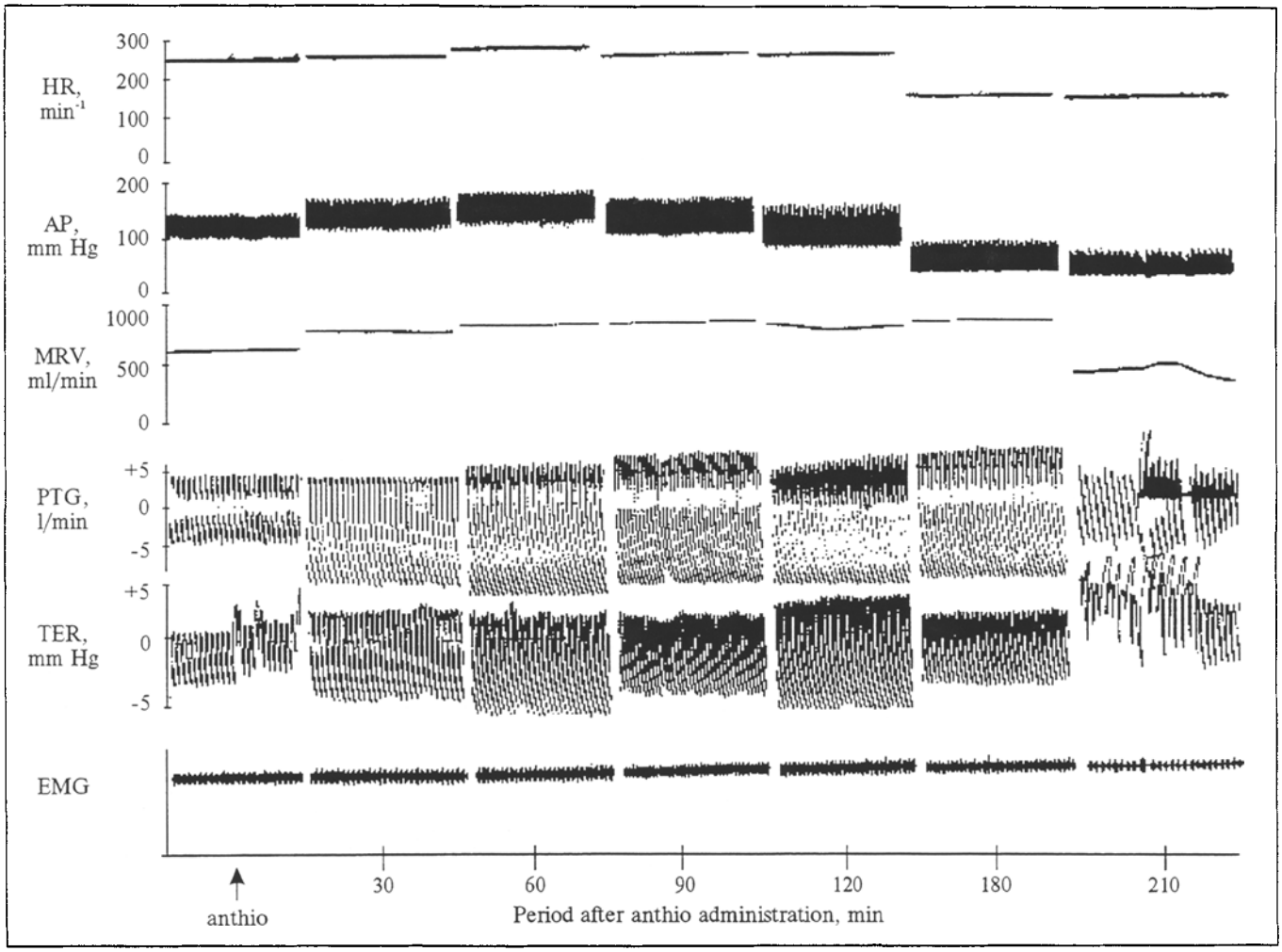

Fig. 2. Effect of Anthio on EMG of the diaphragm, hemodynamics, and ventilation of the lungs in narcotized cats. *PTG*: pneumotachogram; *EMG*: electromyogram of the diaphragm; periods elapsed in min.

ing 5-6 ml. The preparation of animals and methods of measuring vital activity parameters were described in detail previously [9, 10]. In the present study we assessed, besides the parameters examined before, longevity, pulmonary coefficient, and dry residue of the lungs (similarly as previously [9]), and measured the hemoglobin concentration after Sahli and the hematocrit using an Adams-Readacrit ("Clay Adams", USA) microcentrifuge. A shift of the effect of the autonomic nervous system on cardiac activity was assessed from Kerdo's vegetative index (KVI)=(1-RR/HR)×100,

TABLE 2. Circulation Parameters in Narcotized Cats after Administration of Anthio (mean±SEM; $n = 13$)

Parameter	Time, min								
	0	30	60	90	120	150	180	210	240
HR, cycles/min	237±7	233±9	232±9	218±9	209±9*	215±13	200±12*	183±15*	143±38*
AP, mm Hg	126±6	115±5	106±6*	88±6*	74±8*	79±8	65.0±12*	48±5*	30±5
Systolic AP, mm Hg	152±5	141±6	132±7*	110±8*	107±13*	104±11*	90±12*	78±18*	68±10*
Diastolic AP, mm Hg	111±5	99±5	91±7*	69±6*	62±9*	62±8*	43±12*	39±10*	25±5*
Pulse AP, mm Hg	41±2	41±1	41±2	41±2.5	39±4	41±5	47±3	39±5	43±7.5
KVI	53.1±1.8	57.4±1.6	60.7±2.5*	68.4±2.4*	72.1±3.9*	76.0±2.0*	82.4±2.6*	85.4±1.3*	—

TABLE 3. Blood Characteristics in Narcotized Cats after Administration of Anthio ($M \pm m$; $n = 13$)

Parameter	Time, min								
	0	30	60	90	120	150	180	210	240
Hematocrit, %	42.6±1.1	45.5±1.2	48.1±1.7*	48.3±2.0*	48.2±2.5	50.0±3.2*	46.5±1.8	47.7±3.2	48.3±4.7
Hemoglobin concentration, g%	14.3±0.4	15.1±0.4	16.0±0.6*	16.1±0.7*	16.1±0.8	16.7±1.1	15.5±0.6	15.9±1.1	16.1±1.5
pH_a	7.29±0.02	7.25±0.02	7.23±0.03	7.19±0.03*	7.15±0.04*	7.15±0.05*	7.14±0.06*	7.06±0.08*	7.02±0.04*
P_aCO_2, mm Hg	29.4±1.2	26.1±0.8*	25.1±1.1*	23.6±1.5*	22.7±1.4*	22.1±1.5*	21.4±1.5*	24.7±4.2	26.5±6.0
P_aO_2, mm Hg	86.2±2.3	87.1±3.5	88.0±3.0	88.4±3.0	90.8±2.9	89.8±3.3	92.5±4.8	87.0±6.1	81.8±9.5
S_aO_2, %	94.7±0.4	93.9±0.8	93.5±0.9	92.5±1.6	93.0±0.8	92.8±0.8	93.1±1.3	90.0±4.8	85.7±5.1
Oxygen content, mM	8.5±0.2	8.9±0.2	9.4±0.3	9.3±0.4	9.4±0.5	9.8±0.6	9.2±0.3	9.4±0.6	8.7±1.0
Buffer bases shift, mM	−11.5±0.9	−14.9±0.9*	−16.5±1.1*	−18.8±1.1*	−20.6±1.4*	−21.0±2.2*	−21.2±2.4*	−23.9±2.1*	−25.4±0.3*

where RR is the respiratory rate and HR the heart rate [6]. The data were statistically processed using the Student t test.

RESULTS

It is noteworthy, first of all, that although we used a moderate dose of Anthio, all the cats died an average 183±17 min after the agent was administered. It may be assumed that narcotized animals become more sensitive to Anthio due to the reduced compensatory adaptive potential and may therefore be used as a convenient model for studies of a weakened organism's response. The conclusion about a weakening effect of narcosis on the body may be drawn from the fact that a similar administration of Anthio to non-narcotized cats does not always have a lethal outcome and the majority of animals survive for at least several days (unpublished observations). Autopsy of experimental animals showed, among other things, that the values of the pulmonary coefficient and dry residue of the lungs (6.03±0.38 g/kg and 23.7±0.4%, respectively) were close to the normal values (6.30±0.54 and 24.6±1.5, respectively), but the lungs themselves exhibited an irregular mosaic of whitish spots interspersed with lilac-pink ones, this indicating disorders in the pulmonary circulation and being in line with the data on disordered pulmonary bloodflow under the effect of OPC [8].

Table 1 and Figs. 1 and 2 show that respiration after the administration of Anthio changes little on the whole: the respiration rate (RR) is stably maintained at a level close to the initial, but the minute respiratory volume (MRV) shows a trend to increase due to corresponding changes in respiration depth which, however, become reliable only 3 h after the onset of the agent's effect. The maximal expiration rate was also virtually unchanged in our experiments, but the maximal inhalation rate was increased twofold and more starting from the first hour after Anthio administration. The increased maximal inhalation rate persisted over the course of virtually the entire period of agent action and only 3 h later did a regressive course of this value set in, which continued till the death of the animal. A similar time course and degree of changes were observed under such conditions when the amplitude of transesophageal pressure (TEP) was recorded, this time course reflecting the integrative activity of the respiratory muscles: TEP increased due to an increase of the inspiratory component of the respiration cycle (Figs. 1 and 2).

The TEP curve represented on Figs. 1 and 2 shows convulsive upward outputs toward a pressure increase which need to be explained. To our mind, such jolts developing immediately after Anthio administration occur due to a rise of pressure in the lower portion of the esophagus and stomach, while 2-2.5 h later they reflect vomiting movements emerging at the stage of decompensation because of developing intoxication of the body.

Changes in the pneumotachogram (PTG) and TEP parameters after administration of Anthio manifest themselves during analysis of the time course of electrical activity of the respiratory muscles (Fig. 3). It is characteristic that EMG activity of thoracic and abdominal muscles, particularly of expiratory muscles, abates as early as starting from the 30th min after the onset of agent action, this being true of both the phasic (respiratory) and the postural-tonic activities of these muscles. A lower activity of the thoracic and ab-

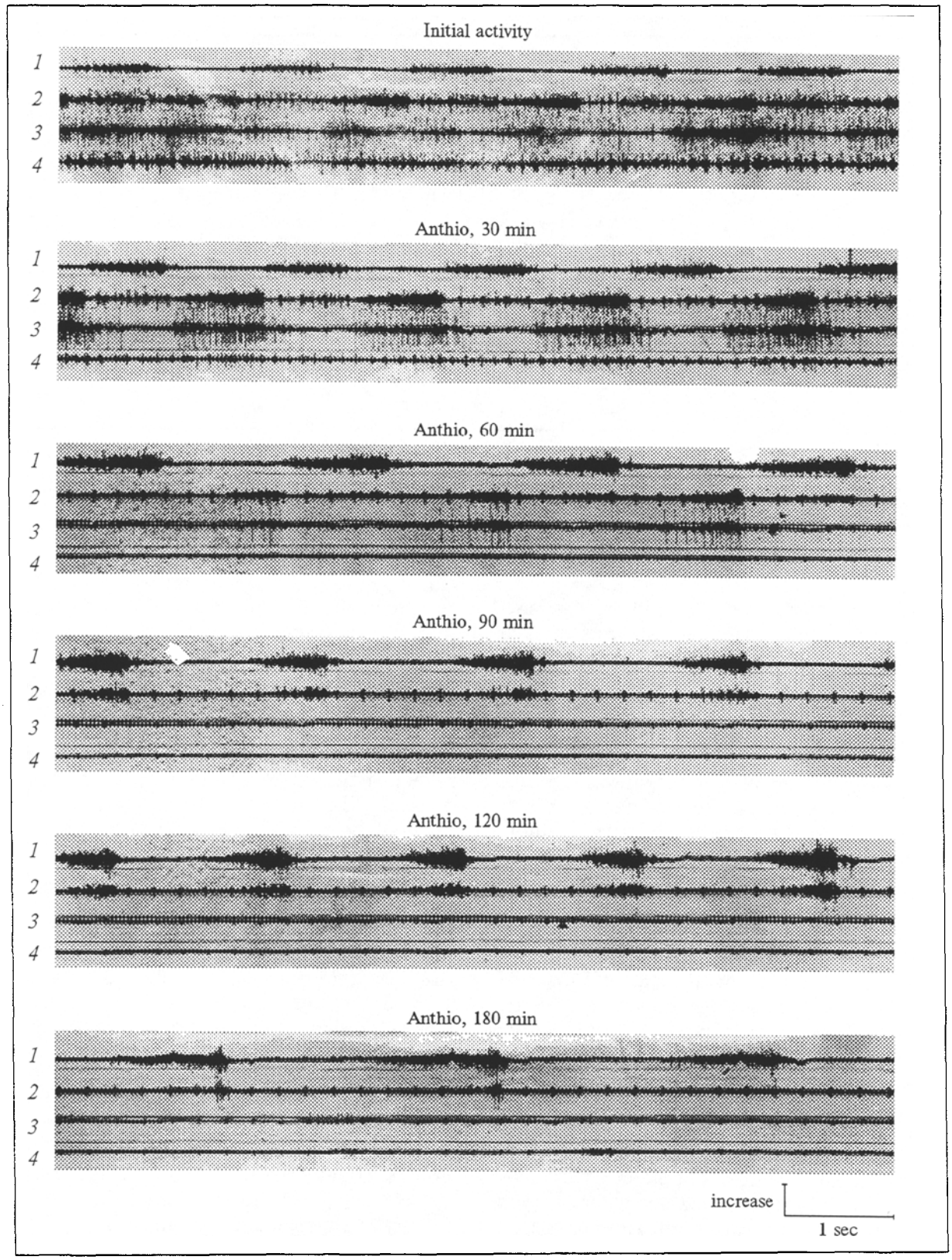

Fig. 3. Changes in electrical activity of respiratory muscles after administration of Anthio. *1*) diaphragm; *2*) intercostal muscle (5th–6th intercostal space); *3*) intercostal muscle (9th–10th intercostal space); *4*) oblique

dominal muscles during this period is compensated for by increased activity of the diaphragm, which under such conditions provides for the greater part of the respiratory volume (RV). Hence, the greater

deviations on the inspiratory portion of the PTG and TEP curves are explained by increased diaphragmatic activity, which is maintained until the state of decompensation develops.

Note that pronounced changes in pressure amplitude in the esophagus (thoracic cavity) after administration of Anthio do not lead to corresponding RV changes. This could be due to increased resistance to air flow in the lower respiratory tract because of bronchospasm and(or) swelling of tracheobronchial mucosa which are usually seen at autopsy.

Changes in systemic hemodynamic parameters after Anthio administration are more expressed than those in respiration values (Table 2): except for the pulse pressure amplitude, which remains unchanged over the course of the entire experiment, the rest of the parameters are markedly changed. The most pronounced of these shifts is arterial pressure reduction starting from the 60th min after Anthio administration, which is paralleled by an HR reduction which somewhat lags behind the arterial pressure reduction. These parameters, indicating depression of the cardiovascular system, confirm a possible effect of Anthio on its cholinoreceptors. The increase of KVI is particularly interesting in this connection, suggesting a possibility of an increased effect on the heart activity of the sympathetic component of the autonomic nervous system evidently directed at compensation of the increased cholinergic effects. We did indeed observe in some experiments an HR increase which seemed to be mediated by increased sympathetic effects (Fig. 2). Hence, the total effect is determined by the balance between the central and peripheral cholinergic prolonged action of Anthio and the central compensating activation of the sympathetic system.

Such shifts in the autonomic nervous system tonus, along with the histotoxic effect of Anthio and resultant tissue hypoxia, may account for the higher hematocrit and, hence, the increased blood hemoglobin concentration (Table 3) observed during the development of compensatory reactions. That is why, although the values of hemoglobin saturation with oxygen and the oxygen tension in the arterial blood after administration of Anthio remain at a level close to the initial, the oxygen content in the blood increases (reliably only 1 h after administration). The increased hematocrit under such conditions has a double effect: on the one hand, it is conducive to increasing the oxygen capacity of the blood, this being a favorable factor in hypoxic states of the organism, and on the other, it increases the viscosity of the blood, thus impeding its flow in the microvessels. The S_aO_2 value is maintained at a constant level in the presence f changed pH_a and P_aCO_2, diversely influencing hemoglobin capacity to capture oxygen: the carbon dioxide tension in the arterial blood drops until decompensation disorders develop (this increasing hemoglobin affinity for oxygen), and the arterial blood reaction shifts towards acidosis of a metabolic type (decreasing the affinity). The resultant hypocapnia, representing the response of the respiratory system to acidosis, is mediated by the deeper respiration developing after Anthio administration. By its value, acidosis is decompensated (reaction shift to approximately pH 7) and is attended by a drastic deficit of buffer bases of the blood: -25.4±0.3 mmole 4 h after Anthio administration (Table 3).

We consider that acidosis development after administration of Anthio is a result of disorders in tissue respiration related to disordered mitochondrial function and(or) structure, which is confirmed by some published data [3,4,11]. These data may explain the death of pentobarbital-anesthetized animals after administration of Anthio in a dose equal to 20% of LD_{50}, since barbiturates and OPC are known to synergistically depress mitochondrial activity [4].

Hence, combined pathogenetically based treatment of subjects poisoned with OPC should include, besides the routinely used cholinolytics and cholinesterase reactivators, measures aimed at improving the resistance of mitochondrial activity and structure.

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