Effects of Calcium and Its Antagonists on Hemodynamics and Respiration

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 122, No. 8, pp. 138-143, August, 1996
Original article submitted July 10, 1995

Acute tests on cats under Nembutal anesthesia show that intravenous injection of Ca^{2+} causes pathological respiration of the apneustic type and slight rises in pulmonary and arterial pressures. The calcium channel blockers verapamil and nifedipine decrease the amplitude of respiratory movements, increase the respiration rate and pulmonary pulse pressure, and lower systemic pressure. The introduction of verapamil or nifedipine into the fourth ventricle of the brain does not alter respiration or hemodynamics, whereas the introduction of Ca^{2+} leads to irreversible respiratory standstill. Hemodynamic parameters decrease 2-3 min after the respiratory standstill.

Key Words: *hemodynamics; respiration; calcium; calcium channel blockers; ultrasound*

Acute systemic hypoxia induces in mammals biphasic changes in respiration, with the initial enhancement of respiration being followed by its inhibition culminating in respiratory standstill (apnea). The major mechanisms responsible for these disorders of the central respiratory rhythm in hypoxia are not completely understood and continue to be under study [12,13]. An important role here is played by disturbances of the extracellular and intracellular ionic media arising in hypoxia. It has been shown that hypoxia is accompanied, along with other changes, by accumulation of intracellular Ca^{2+} which enters the cell from the extracellular medium and exits from intracellular sites of its deposition [1,11]. Raised intracellular Ca^{2+} may act as a toxin and impair cell functions, resulting, in particular, in damage to respiratory neurons and in a disturbance of the respiratory rhythm. The cardiovascular system is more resistant to hypoxia: it usually ceases to function several minutes after the respiratory standstill [7].

This study was undertaken to answer the question of whether elevated Ca^{2+} concentration can reproduce the effects of hypoxia such as changes in hemodynamics and respiration due to the direct action of hypoxia and to examine the effects on hemodynamics and respiration of the calcium channel blockers verapamil and nifedipine.

MATERIALS AND METHODS

A total of 16 acute tests were performed on 16 spontaneously breathing male and female cats (body weight 2.5-4.4 kg) with closed chest under Nembutal anesthesia (40-50 mg/kg intraperitoneally). Linear and volume blood flow rates in the ascending aorta and arterial cone were estimated using an ultrasonic method [4,6]. Arterial pressure (AP) in the pulmonary and femoral arteries was measured with an electric manometer. Under artificial pulmonary ventilation, ultrasonic sensors were placed on the appropriate vessels, the chest was sutured in layers, and the cats were transferred to spontaneous respiration. Respiratory excursions of the chest were recorded using a tensometric sensor.

In addition to exerting direct influences on brain structures, Ca^{2+} and its blockers can act on these structures indirectly, by altering blood supply to the brain which in cats is effected via the common ca-

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0007-4888/96/0008-0772$15.00

rotid artery and especially the internal mandibular artery [3]. In five cats, linear and volume blood flow rates were measured using miniature ultrasonic sensors with internal diameters of 1.5 and 0.5 mm.

We studied the effects exerted on the above-mentioned parameters by intravenously injected calcium chloride (35-70 mg/kg in a volume of 2 ml), verapamil (0.6-0.8 mg/kg) and nifedipine (1 mg/kg), both in a volume of 1-1.5 ml. Ca^{2+} (6-8 mg/kg) and its blockers (0.1-0.15 mg/kg) were injected centrally, into the fourth brain ventricle, in a volume of 200 μl. Preliminarily, the same volume of isotonic sodium chloride solution was injected into the fourth ventricle for control purposes.

RESULTS

Ca^{2+} injected intravenously in a dose of 0.35 mg/kg decreased the frequency and amplitude of respiratory movements. After a much larger dose (60-70 mg/kg) or a second injection of the same dose as before, pathological respiration of the apneustic type usually occurred (decreased respiratory rate because of considerably prolonged inspirations) (Fig. 1, *a*). In some tests, periodic respiration of the Cheyne—Stokes type was observed, with superimposed inspirations (gasping). It should be noted that the Ca^{2+} dose required to produce an abnormal respiratory pattern depends on the general condition of the animal during the experiment (on systemic and AP levels, depth of anesthesia, etc.).

Large Ca^{2+} doses (120-200 mg/kg) were shown to cause ventricular fibrillation in experimental animals [14]. In our study, Ca^{2+} doses 2 to 3 times lower were found to be required to disturb the respiratory rhythm. In some cats, intravenous Ca^{2+} injection was followed by an extrasystole of shorter duration than the disturbance of respiratory rhythm. With the Ca^{2+} doses used, hemodynamic changes were inconstant and moderate. Pulmonary AP rose, on average, to 130% of its baseline level. In some cats, the mean pulmonary AP remained unchanged, but the pulse pressure rose as a result of lowered diastolic and elevated systolic AP. Resistance of the pulmonary vascular bed showed no significant change.

Systemic AP rose in most cats to 127% of the baseline level on average, while in 4 animals it fell, on average, to 80% of that level.

Cardiac output rose or declined in different cats by 15-25% relative to baseline and remained unchanged in 3 cats. In 4 cats, a well-defined, though transient, disturbance of the balance between the right and left ventricular outputs was observed: the right ventricular output increased, whereas the left ventricle output remained unchanged or even decreased — a phenomenon possibly associated with alterations in venous return [8]. The upset balance between right and left ventricular outputs was not related to the severity of respiratory disorders.

Blood supply to the brain increased to 125% of the baseline level in 3 cats and did not change in 2. The heart rate remained unchanged in most cats, but differed by 10-20% from baseline level in some. A considerable increase in heart rate was only observed with respiration of the gasping type. It should be pointed out that alterations in hemodynamic parameters after the second Ca^{2+} injection differed from those after the first or did not occur at all. The respiratory pattern became normal 15-20 min after the second Ca^{2+} injection. Hemodynamic parameters returned to normal more rapidly (after 2-3 min) than did respiration.

Preinjecting cats with verapamil or nifedipine failed to prevent completely respiratory rhythm disturbances after the subsequent Ca^{2+} injection, but a higher Ca^{2+} dose was required to produce these and, moreover, the respiratory rhythm returned toward normal more rapidly. The calcium blockers also failed to eliminate the apneusis that arose after Ca^{2+} injection.

Ca^{2+} injection into the fourth ventricle in a dose of 0.1 to 0.15 mg/kg resulted in apneusis with subsequent restoration of the initial respiratory rhythm. A second Ca^{2+} injection in the same doses led to apneusis and respiratory standstill at inspiration 10 sec to 5 min postinjection (Fig. 1, *b* and *c*). In some cats, apnea was observed even after the first Ca^{2+} injection, and the injection of verapamil or nifedipine in these tests did not result in restoration of respiration (Fig. 1, *b*). The calcium channel blocker injected into the fourth ventricle prevented the development of apnea after the subsequent Ca^{2+} injection.

There are close functional links between the centers regulating respiration and cardiovascular activity [2,5,11]. Centrally injected Ca^{2+}, which causes respiratory standstill, could therefore be expected to have an immediate impact on hemodynamic parameters. Alterations in these, however, occurred 2-3 min after the respiratory standstill caused by Ca^{2+}, i.e., in the same interval as in ordinary asphyxia (Fig. 1, *b* and *c*). As in the case of intravenous Ca^{2+} injection, larger doses of this ion are possibly required to impair hemodynamics after its central administration.

When cats with the apneusis induced by intravenous Ca^{2+} began to breathe a hypoxic gaseous mixture (3-5% O_2 in nitrogen), their respiratory rhythm returned to normal and their response to the hypoxia became similar to that usually observed: the respiratory frequency and amplitude increased, deep intercalated inspirations were observed, and the pul-

monary AP and pulmonary vascular resistance rose (Fig. 2, *a* and *b*). However, the respiratory standstill in hypoxic cats and the subsequent resumption of respiration after the apnea were followed after 10-15 min by a recurrent apneusis or other pathological forms of respiration that had been observed before hypoxia (Fig. 2, *c*).

It has been reported that cats with denervated peripheral chemoreceptors developed central apnea during hypoxia, whereas those with intact chemore-

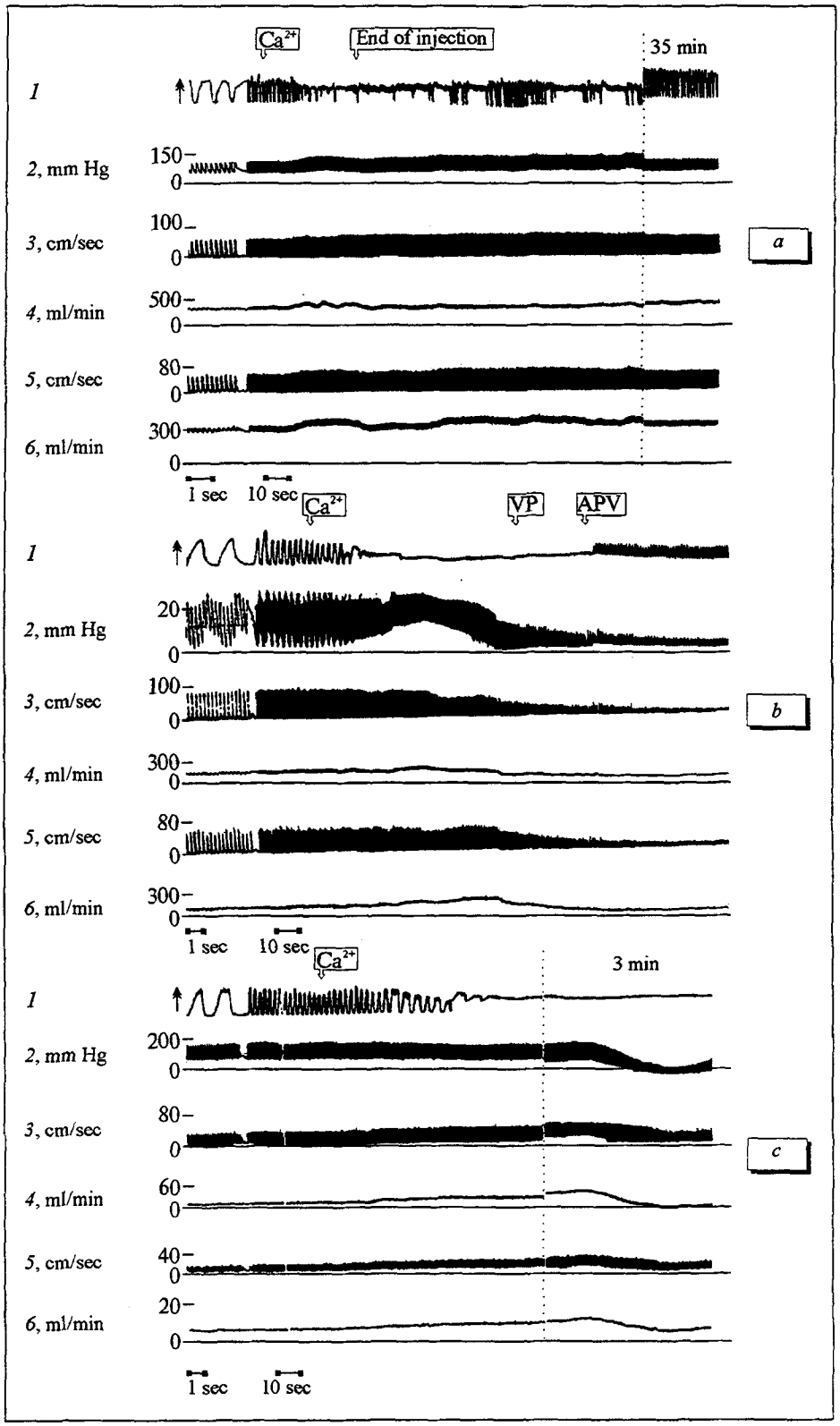

Fig. 1. Effects of intravenously (*a*) and centrally (*b* and *c*) injected Ca^{2+} on hemodynamics and respiration. *1*) respiration; *2*) arterial pressure in the femoral (*a* and *c*) and pulmonary (*b*) arteries; *3*) linear blood flow rate in the ascending aorta (*a* and *b*) and carotid artery (*c*); *4*) volume blood flow rate in the aorta (*a* and *b*) and carotid artery (*c*); *5*) liner blood flow rate in the arterial cone (*a* and *b*) and internal maxillary artery (*c*); *6*) volume blood flow rate in the arterial cone (*a* and *b*) and internal maxillary artery (*c*). Here and in Figs. 2 and 3: the line under each curve indicates zero level; arrows show the beginning and end of Ca^{2+} or verapamil (VP) injection; figures in the upper part of the figures are the times elapsing after injection; up pointing arrows denote inspiration. APV = artificial pulmonary ventilation.

ceptors showed only inhibition of respiratory neurons whose rhythmic activity was preserved [13]. The restoration of rhythmic breathing in animals with hypoxia in the presence of apneusis induced by Ca^{2+} administration is likely to be associated with the afferent signals from peripheral chemoreceptors due to a low pO_2 of arterial blood.

There is also evidence that hypoxia may exert an antiarrhythmic effect on the heart; thus, ventricular fibrillation induced by electric stimulation in a

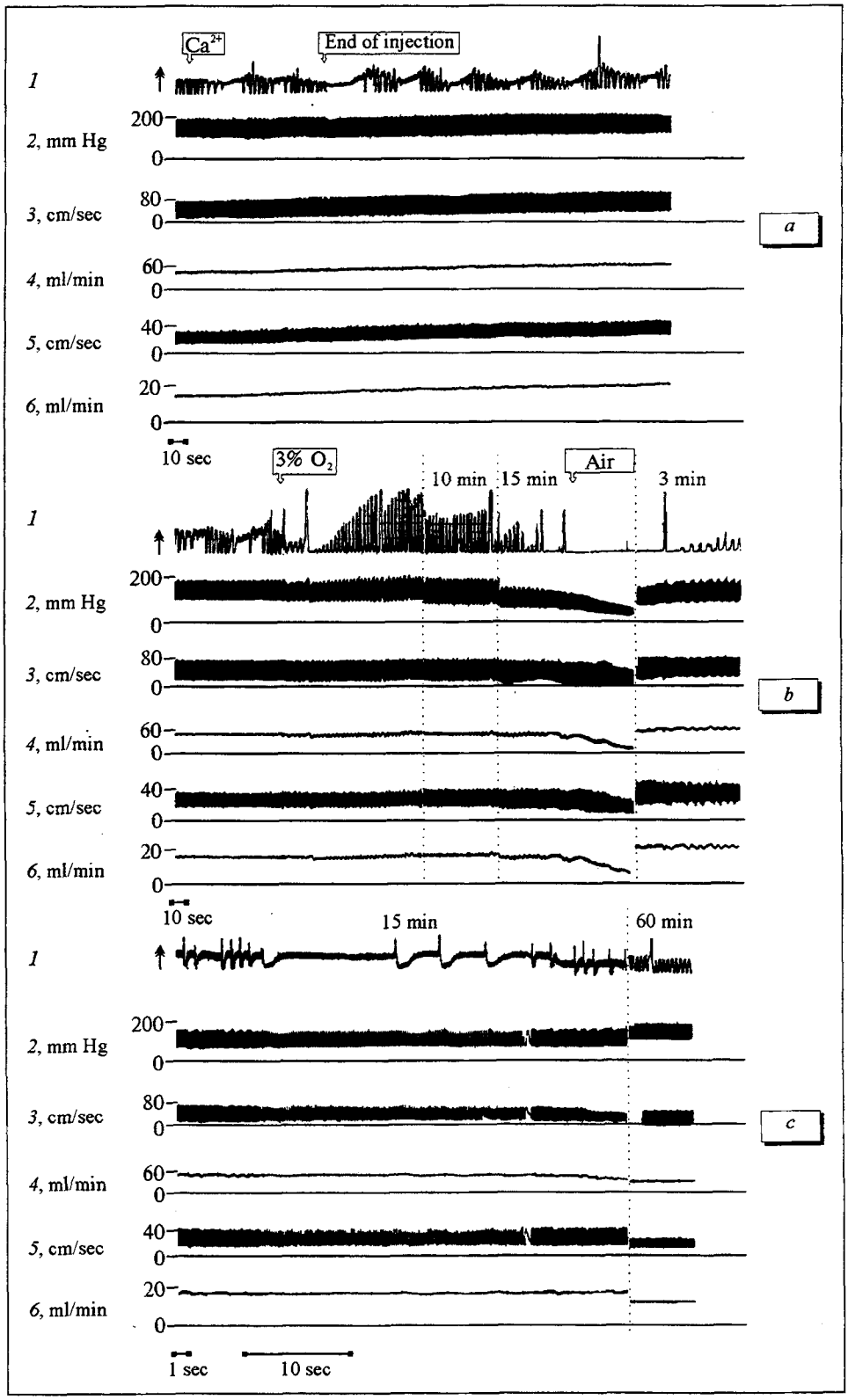

Fig. 2. Effects of hypoxia (*b*) on hemodynamics and respiration after intravenous Ca^{2+} injection (*a*) and during recovery (*c*). *1*) respiration; *2*) AP in the femoral artery; *3*) linear blood flow rate in the carotid artery; *4*) volume blood rate in the carotid artery; *5*) linear blood flow rate in the internal maxillary artery; *6*) volume blood flow rate in the internal maxillary artery.

rabbit was abolished if perfusion with an oxygen-saturated liquid was replaced by perfusion with a nitrogen-saturated medium [9,10].

Intravenous injection of verapamil or nifedipine usually resulted in a decreased amplitude of respiratory movements and increased respiratory rate (Fig. 3, *a*). Systemic AP dropped, on average to 70% of its initial value. The mean AP in the pulmonary artery did not change markedly in most cases, but the pulse pressure rose. The heart rate changed by not more than 20%.

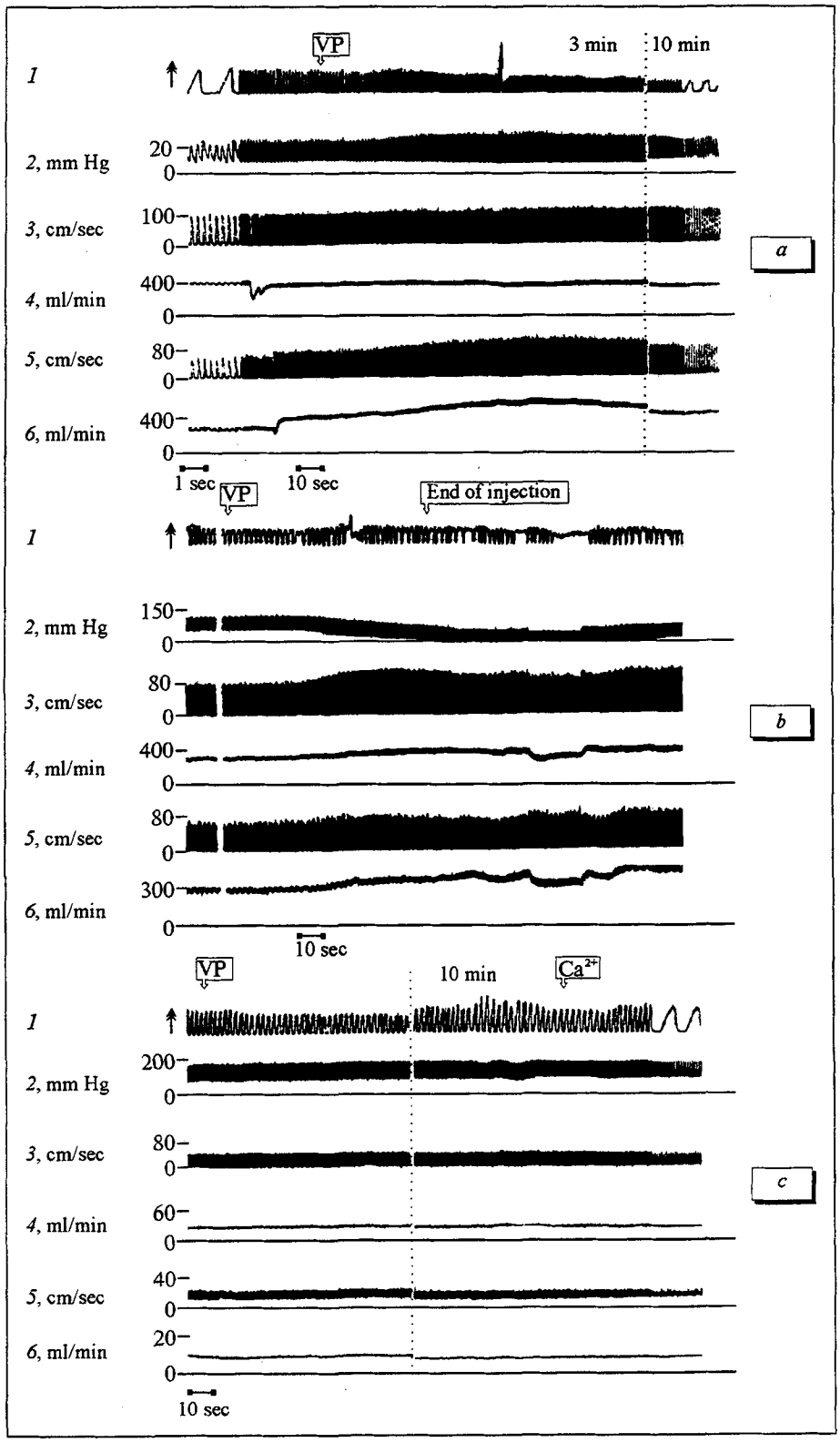

Fig. 3. Effects of intravenously and centrally injected Ca^{2+} antagonists on hemodynamics and respiration. *a*) verapamil (VP) injected intravenously before Ca^{2+}; *b*) VP injected intravenously after Ca^{2+}; *c*) VP injected into the fourth ventricle followed by Ca^{2+} injection 10 min later. *1*) respiration; *2*) arterial pressure in the pulmonary (*a*) and femoral (*b* and *c*) arteries; *3*) linear blood flow rate in the ascending aorta (*a* and *b*) and carotid artery (*c*); *4*) volume blood flow rate in the aorta (*a* and *b*) and carotid artery (*c*); *5*) linear blood flow rate in the arterial cone (*a* and *b*) and internal maxillary artery (*c*); *6*) volume blood flow rate in the arterial cone (*a* and *b*) and internal maxillary artery (*c*).

Blood supply to the brain increased 1.5- to 2-fold. Alterations in cardiac output depended on whether the calcium channel blocker was administered before or after Ca^{2+} injection. When verapamil or nifedipine were given before intravenous Ca^{2+} injection, cardiac output usually remained unchanged. When they were given after intravenous Ca^{2+} injection, a transient reduction of cardiac output to 80% of its initial level was observed in some cats and its increase to 130-140% of the initial level in others. As in the case of exposure to Ca^{2+} alone, the balance between right and left ventricular outputs was upset for a short time (Fig. 3, *a* and *b*). If the blockers were administered after Ca^{2+} and the respiratory disturbances they produced had already disappeared, then verapamil or nifedipine administration could induce respiratory changes of the apneustic type (Fig. 3, *b*). Respiratory standstill occurred in one cat after intravenous verapamil injection and also in one after nifedipine injection.

Verapamil or nifedipine introduced into the fourth ventricle did not, as a rule, cause alterations in the respiratory rhythm or in hemodynamics in the doses used; in some cats, however, the amplitude of respiratory movements decreased (Fig. 3, *c*).

In conclusion, our study shows that Ca^{2+} elicits well-defined and consistent changes in respiration and inconsistent changes or no changes at all in hemodynamics. Intravenously injected Ca^{2+} results in pathological respiration of the apneustic type, usually during the period of recovery after exposure to acute hypoxic hypoxia. After a central Ca^{2+} injection, there occurs respiratory standstill under the influence of acute hypoxia. Intravenous Ca^{2+} injection also results in a slight elevation of pulmonary AP.

REFERENCES

1. M. V. Bilenko, *Ischemia- and Reperfusion-Induced Injuries to Organs* [in Russian], Moscow (1989).
2. R. Sh. Gabdrakhmanov, Yu. M. Popov, and N. A. Gordievskaya, in: *The Respiratory Center: Functional Organization and Links with Other Systems* [in Russian], Kuibyshev (1990).
3. B. N. Klosovskii, *Circulation of Blood in the Brain* [in Russian], Moscow (1951).
4. D. D. Matsievskii, *Byull. Eksp. Biol. Med.*, **114**, No. 7, 19 (1992).
5. V. M. Pokrovskii, V. G. Abushkevich, and A. I. Dashkovskii, *Fiziol. Zh. SSSR*, **76**, 1340 (1990).
6. N. V. Sanotskaya and D. D. Matsievskii, *Byull. Eksp. Biol. Med.*, **94**, No. 12, 119 (1982).
7. N. V. Sanotskaya, D. D. Matsievskii, and S. O. Aleinikov, *Byull. Eksp. Biol. Med.*, **115**, No. 6, 579 (1993).
8. B. I. Tkachenko, *Venous Circulation* [in Russian], Leningrad (1979).
9. J. H. Burn and P. J. Goodford, *J. Physiol. (London)*, **137**, 20 (1957).
10. P. J. Goodford, *Br. J. Pharmacol.*, **13**, 144 (1958).
11. D. E. Millhom, *J. Physiol. (London)*, **370**, 217 (1986).
12. D. W. Richter, in: *Chemoreceptors and Reflexes in Breathing: Cellular and Molecular Aspects*, Eds. S. Lahiri *et al.*, Oxford (1989), p. 267.
13. D. W. Richter, A. Bischop, K. Anders, *et al.*, *J. Physiol. (London)*, **443**, 231 (1991).
14. L. Szekeres and Gy. J. Papp, *Experimental Cardiac Arrhythmias and Antiarrythmic Drugs*, Budapest (1971).