Neurohormonal Changes in Acute Pulmonary Embolism (An Experimental and Clinical Study)

M. S. Tverskaya, L. D. Makarova, N. A. Sergeeva, A. O. Virganskii, and S. Yu. Savvina

UDC 616.127-091+616.131-088.331.07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 7, pp. 29-31, July, 1993. Original article submitted February 11, 1993

Key Words: *pulmonary embolism; sympathicoadrenal system; adrenocortical system*

Acute pulmonary embolism (PE) is accompanied by severe pathophysiological changes that may alter the status of neurohormonal regulatory systems. Examination of the patient permits detection of only those changes that occur 12 or more hours after the onset of PE [7]. In contrast, examination of animals with experimentally produced PE enables the investigator to study neurohormonal reactions during the first few hours after its inducement as well as to compare the test and control animals.

In this work, we examined the state of the sympathicoadrenal and adrenocortical systems in animals with massive PE and in patients with massive PE or with embolism of pulmonary artery branches (nonmassive PE).

MATERIALS AND METHODS

For the experimental study, 30 mongrel dogs weighing 15-20 kg were used. Catheterization of the heart and blood vessels was carried out (without opening the chest and without artificial ventilation) under general anesthesia with sodium thiopental (20 mg/kg intravenously) after premedication with promedol (20 mg/kg intramuscularly). The catheterization procedure has been described previously, as have been the methods used to record the hemodynamic parameters and to produce PE [3]. The embolization led to a considerable and sustained elevation of right ventricular pressure, which reached 68.0±5.0 mm Hg 6 h after the onset of PE. All dogs were found to have bilateral embolism involving the main pulmonary arteries as well as lobar arterial vessels. The high pulmonary hypertension and the large extent of embolic obstruction permitted us to rate the PE as massive [6]. Blood samples for measuring biochemical parameters were taken from the right ventricle immediately after the completion of cardiac catheterization (Fig. 1, *a*) and also 3 h and 6 h after embolization (Fig. 1, *b* and *c*). Control dogs underwent the same catheterization procedure as did test dogs but without embolization, and their blood was sampled at the same times as in test dogs.

The clinical study was carried out on 37 patients with PE hospitalized 12 hours to 23 days after its onset. The diagnosis of PE had been confirmed, in all cases, by perfusion scanning of the lungs and by angiopulmonography, which was preceded by measurement of the pulmonary pressure. The angiopulmonograms were used to localize thromboemboli and to determine the extent of embolic obstruction by calculating Miller's angiographic index of its severity [9]. According to the extent and nature of the embolic obstruction, the patients were divided into two groups. In group 1, all patients (n=8, mean age 43.0±4.0 years) had emboli in lobar and major segmental branches of the pulmonary arteries, either bilaterally (n=3) or

Russian Medical University, Moscow. (Presented by V. S. Savel'ev, Member of the Russian Academy of Medical Sciences)

0007-4888/93/0007-0794$12.50 ©1993 Plenum Publishing Corporation

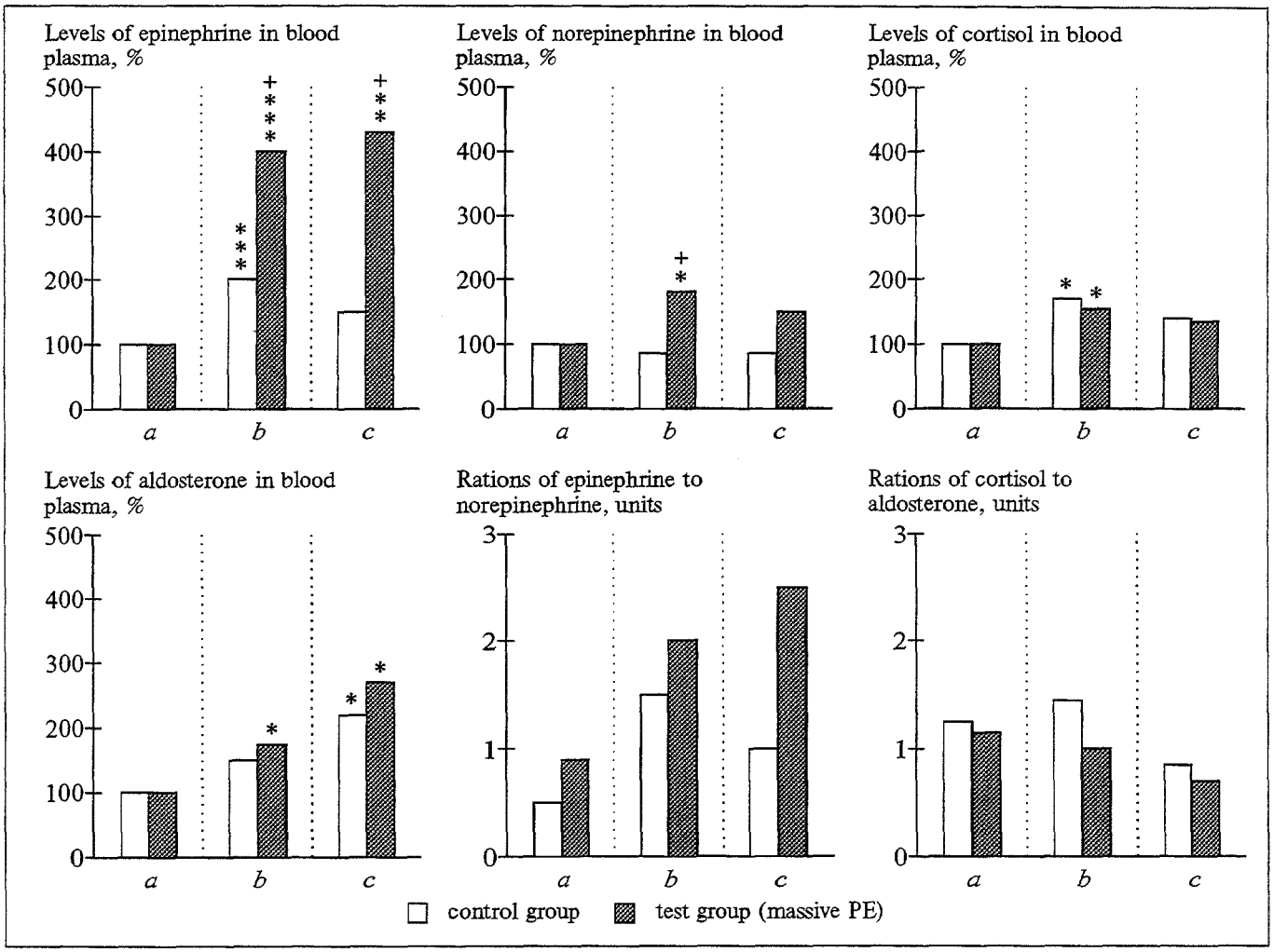

Fig. 1. Neurohormonal changes in experimental massive pulmonary embolism (PE). *a*) levels of respective hormones or ratios after catheterization of heart and before production of PE; *b* and *c*) 3 h and 6 h after PE production or after the control examination. Significant differences from baseline values are denoted by asterisks (*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$) and those from control values, by crosses ($p<0.05$).

unilaterally. The angiographic index in these patients did not exceed 16 points (mean, 13.5±1.7 points) and the pulmonary artery systolic pressure ranged from 18.0 to 42.0 mm Hg (mean, 33.0±3.0 mm Hg). In group 2, all patients (n=29, mean age 52.0±2.0 years) had emboli in the main pulmonary arteries and lobar arterial vessels; in 27 of them PE was bilateral. The angiographic index in this group was more than 16 points (mean, 24.9±0.7) and the pulmonary artery systolic pressure ranged from 36.0 to 84.0 mm Hg (mean, 61.0±3.0 mm Hg). PE in group 2 was therefore rated as massive [6]. It should be stressed that the severity of PE in this group was similar to that in the group of dogs with experimentally produced PE. Biochemical parameters were measured in mixed venous blood samples taken during catheterization of the right heart, which in patients of both groups was performed after premedication with promedol (1 ml of a 2% solution per kg body weight). The control group consisted of 20 essentially healthy volunteers aged 18-25 years, in whom blood for biochemical examination was taken from the ulnar vein.

The epinephrine (E) and norepinephrine (NE) concentrations in the blood plasma were determined by radioimmunoassay using a standard reagent kit (Chemapol, Czechoslovakia). Blood levels of ACTH and cortisol were measured using kits manufactured by Amersham and Ciba-Corning (England) and those of aldosterone, using reagents purchased from Cea-Ire-Sorin (France).

The results were processed by methods of mathematical statistics using Student's t test to assess the significance of the differences.

RESULTS

Experimental study. In control dogs, activation of the hormonal component of the sympathicoadrenal

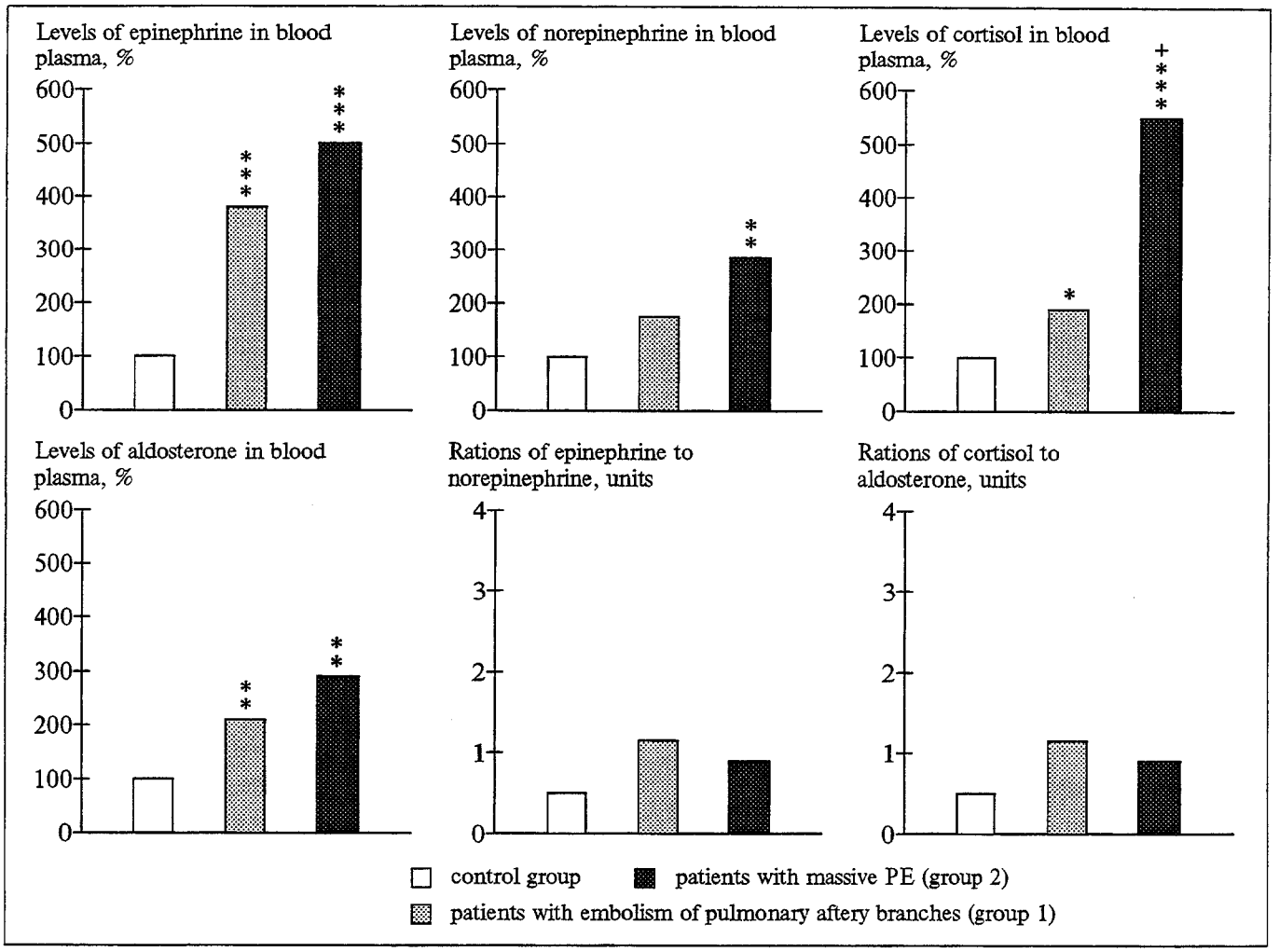

Fig. 2. Neurohormonal changes in patients with acute pulmonary embolism. Significant differences from the control group are denoted by asterisks (*: $p<0.05$,**: $p<0.01$,***: $p<0.001$) and that between groups 1 and 2, by cross ($p<0.05$).

system (SAS) was observed (Fig. 1). In these dogs, reactions of the adrenal medulla to the concentration were not paralleled by those of the sympathetic nervous system, as was indicated by the negative correlation noted between blood levels of E and NE 3 h after the catheterization ($r=-0.63$; $p<0.05$). At that time, there was also observed a moderate increase in the secretory activity of cells in the fascicular and glomerular zones of the adrenal cortex. At 6 h, the blood levels of aldosterone were increased, as they were at 3 h, while those of E and cortisol tended to decrease. The correlation analysis demonstrated a positive correlation ($r=0.89$; $p<0.001$) between changes in the blood levels of E and aldosterone during 6 h postcatheterization.

In dogs with massive PE (Fig. 1), the adrenal system was stimulated more strongly than it was in the control dogs, and the stimulatory effect was still evident 6 h after the production of PE. Unlike in the control dogs, the nervous and hormonal components of the SAS were both activated at that time, as was indicated by the positive correlation between changes in the blood levels of NE and E ($r=0.55$; $p<0.05$). On the other hand, alterations in the blood levels of cortisol and aldosterone were similar to those recorded for control dogs, with shifts toward increased mineralocorticoid activity. The correlation analysis revealed a positive correlation ($r=0.47$; $p<0.05$) between alterations in the blood levels of E and aldosterone during the first 6 h after the onset of PE.

The comparison of hormonal changes in dogs with experimental massive PE and in control dogs led us to conclude that the observed strongly marked stimulation of adrenal medullary cells was largely due to the pathophysiological changes characteristic of massive embolism of pulmonary vessels, but that the increased functional activity of adrenal cortical cells resulted from the action of predominantly nonspecific stress factors such as immobilization of the animal and catheterization of its heart [4,7].

Clinical study. The neurohormonal reactions recorded in patients with acute PE (Fig. 2) were, on the whole, similar to those registered in dogs with experimentally produced PE and involved parallel stimulation of both SAS components, with predominant involvement of the adrenal component, and also increased activities of the fascicular and glomerular zones of the adrenal cortex. In view of the results obtained in dogs and described above, these changes could be regarded as being consequent to the action of both specific and nonspecific factors. The former factors were taken to include the conditions of blood sampling in the patients that might elicit changes characteristic of stress reactions, in particular rises in the blood levels of catecholamines and glucocorticoids [7,8]. The nonspecific factors were considered to include pathophysiological changes occurring in the presence of acute embolic occlusion of pulmonary vessels, notably increased pulmonary arterial pressure, reduced systemic arterial pressure, reduced cardiac output, and hypoxemia [1, 2]. Since the degree to which the nervous and hormonal components of the SAS were activated in the patients did not depend much on the extent of embolic obstruction (the differences between the two groups were insignificant - see Fig. 2, *I* and *II*), this reaction is presumably largely determined by the action of nonspecific factors - a possibility supported by the reported steep rise in blood levels of catecholamines in patients undergoing cardiac catheterization [7]. In contrast, the rise in the blood level of cortisol largely depended on the extent of embolic occlusion (Fig. 2, *III*) and, consequently, was mainly due to the action of specific factors. In patients with massive PE, in contrast to dogs with a relatively short-term massive PE and to patients with nonmassive PE, a substantial shift in the activity of the adrenal cortical cells toward glucocorticoid activity was observed (Fig. 1, *VI* and Fig. 2, *VI*). This led us to conclude that the rise in glucocorticoid activity was due to the concurrent action of two factors, namely the degree and the duration of embolic obstruction. In our patients, variations in cortisol levels corresponded to those in ACTH, whose blood levels in patients of groups 1 and 2 rose by 78.0±22.0% ($p>0.05$) and 248.0±119.0% ($p<0.05$), respectively.

In summary, our combined clinical and experimental study reported here has shown that activities of the sympathicoadrenal and adrenocortical systems are elevated in PE, and that the magnitude of neurohormonal changes detectable in this condition depends on the extent and duration of embolic obstruction. During the first 6 h after the onset of massive PE, the activities of the regulatory systems under study shift so that the relative importance of the adrenal and mineralocorticoid components increases. These shifts appear to reflect the initial phase of the response to massive embolic occlusion and are directed primarily at reversing the systemic hemodynamic changes that arise, such as reductions in arterial pressure and cardiac output [8]. Later on, the relative importance of the glucocorticoid component increases, which is accompanied by stimulation of catabolic reactions and corresponds to the phase at which metabolic processes are redistributed in favor of those providing energy [8]. Also, glucocorticoids, which exert strong antiinflammatory effects [8], counteract increases in vascular permeability and mitigate the damage to cellular and stromal elements which was found to occur in our previous studies of the heart and lungs in cases of acute PE [2,5].

REFERENCES

1. A. O. Virganskii, in: *Massive Embolism of Pulmonary Arteries* [in Russian], Moscow (1990), pp. 62-89.
2. A. O. Virganskii, V. V. Banin, V. A. Klevtsov, *et al.*, *Fiziol. Zh. SSSR*, **76**, № 10, 1355-1360 (1990).
3. A. O. Virganskii, M. S. Tverskaya, and R. V. Rogulenko, *Byull. Eksp. Biol. Med.*, **110**, № 12, 577-580 (1990).
4. F. Z. Meerson, *Pathogenesis and Prevention of Stress-Induced and Ischemic Myocardial Damage* [in Russian], Moscow (1984).
5. M. S. Tverskaya, V. V. Karpova, L. D. Makarova, *et al.*, *Byull. Eksp. Biol. Med.*, **115**, № 4, 347-350 (1993).
6. V. S. Savel'ev, E. G. Yablokov, and A. I. Kirienko, *Thromboembolism of Pulmonary Arteries* [in Russian], Moscow (1979).
7. E. P. Stepanyan, E. I. Yarlykova, and B. A. Kuznetsov, *Energetics of the Operated Heart* [in Russian], Moscow (1978).
8. J. Tepperman and H. Tepperman, *Metabolic and Endocrine Physiology*, Chicago (1987).
9. G. A. H. Miller, G. C. Sutton, I. H. Kerr, *et al.*, *Brit. Med. J.*, **2**, 681-684 (1971).