EFFECT OF PROPRANOLOL ON DEVELOPMENT OF PULMONARY EDEMA AND ON PULMONARY HEMODYNAMICS FOLLOWING NORADRENALIN INJECTION

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Activation of the sympathetic nervous system during stress is an important factor triggering the development of pulmonary edema (PE) in cardiologic patients [3]. At the same time, we know that the development of PE is a side effect, dangerous for the patient's life, associated with the use of β-adrenoblockers in clinical cardiology [2]. According to our own data, neither stimulation nor blockade of β-adrenoreceptors leads to the development of PE in rats, although administration of propranolol increases the volume of blood in the pulmonary circulation, especially against a background of hypervolemia [5].

Administration of propranolol to patients with pheochromocytoma can provoke the development of PE [13]. The aim of the present investigation was to study the effect of propranolol on the results of functional loading with noradrenalin in order to reveal the role of the sympathetic nervous system in changes in the pulmonary hemodynamics and resistance of the lungs to the development of PE.

EXPERIMENTAL METHOD

Experiments were carried our on 60 albino rats, 20 guinea pigs, and 20 cats. Propranolol was injected intravenously 20 min before noradrenalin (NA). Experiments on rats and guinea pigs were conducted under local anesthesia, but on cats under pentobarbital anesthesia (30-40 mg/kg, intraperitoneally). The pulmonary hemodynamics was studied in cats weighing 2.5-4 kg, with an open chest and with artificial ventilation of the lungs, by an ultrasonic method [4] and by means of electronic manometers of an original design [8]. The intensity of PE and the degree of filling of the pulmonary vessels were assessed by the value of the pulmonary coefficient (PC), the dry residue (DR), the volume of edema fluid (EF), and the increase in blood filling (IBF) (in g/kg body weight) [11]. Rats and guinea pigs were killed 30 min after injection of NA by decapitation by guillotine, the cats after 60-65 min by injection of pentobarbital. There were 10 animals in each series.

EXPERIMENTAL RESULTS

Intravenous injection of NA in doses of 0.05-0.1 mg/kg into albino rats did not lead to the development of PE (Table 1). Injection of NA in a dose of 0.5 mg/kg caused the development of marked PE (Table 1, $p < 0.001$). Injection of the same dose, against the background of propranolol (5 mg/kg) led to death of 100% of the rats 3-4 min after injection, with signs of rapidly developing PE (Table 1). The volume of EF was increased compared with the previous group by 54.3% ($p < 0.02$), and IBF showed a very sharp increase of 208.3% ($p < 0.001$), which evidently facilitated the rapid development of PE also. Injection of NA in doses of 0.05-0.1 mg/kg against the background of propranolol (0.05 and 3 mg/kg, respectively) also led to the development of marked PE (Table 1, $p < 0.001$).

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TABLE 1. Effect of Propranolol on Development of PE after Injection of Noradrenalin

Group of experiments	Group compared	PC	DR	EF	IBF
Intact albino rats (1)	—	6,17±0,44	21,85±0,44	0,00±0,12	0,00±0,43
Noradrenalin, 0.5 mg/kg (2)	1—2	14,68±1,06*	14,79±0,71*	5,03±0,65*	3,48±0,51*
Propranolol + noradrenalin (3)	2—3	24,66±1,70*	15,13±0,39	7,76±0,65*	10,73±1,21*
Noradrenalin, 0.1 mg/kg (4)	1—4	7,69±0,26	20,61±0,24	0,39±0,08	1,12±0,26
Propranolol + noradrenalin (5)	4—5	13,36±1,04*	15,63±0,56*	3,98±0,61*	3,21±0,56*
Noradrenalin, 0.05 mg/kg (6)	1—6	5,62±0,14	21,47±0,21	0,07±0,14	—0,62±0,54
Propranolol + noradrenalin (7)	6—7	10,17±0,95*	17,70±0,72*	1,89±0,42*	2,11±0,53*
Intact guinea pigs (8)	—	8,52±0,89	19,98±0,33	0,00±0,15	0,00±0,86
Noradrenalin, 1 mg/kg (9)	8—9	12,90±3,57*	17,54±1,40*	1,56±0,43*	2,82±0,92*
Propranolol + noradrenalin (10)	9—10	21,05±2,08*	14,15±0,64*	6,13±0,62*	6,40±1,01*
Intact cats (11)	—	6,14±0,35	21,80±0,18	0,00±0,13	0,00±0,52
Noradrenalin, 0.5 mg/kg (12)	11—12	6,07±0,41	21,67±0,65	0,03±0,14	—0,11±0,23
Propranolol + noradrenalin (13)	12—13	8,50±0,38*	21,30±0,86	0,24±0,34*	2,13±0,37*

Legend. Asterisk indicates significant differences (values of p given in text).

Injection of NA into guinea pigs in a dose of 1 mg/kg, causing death of 75-80% of the albino rats from PE, did not lead to the development of any marked degree of PE in the animals (EF 1.56 ± 0.43 in guinea pigs compared with 6.76 ± 0.38 in albino rats). Injection of this same dose of NA against the background of propranolol (5 mg/kg) led to death of 100% of these animals with signs of rapidly developing PE (EF 6.13 ± 0.62, $p < 0.001$), with an increase of 127% of blood filling. Thus injection of propranolol increases the sensitivity of the lungs to the edemogenic action of noradrenalin in rats and guinea pigs.

Injection of 0.5 mg/kg of NA into cats did not lead to the development of PE (Table 1). Against the background of propranolol (3 mg/kg) this led to an increase of 40% in PC, mainly due to an increase in blood filling, and not in hydration of the lungs (Table 1).

Investigation of the hemodynamics in cats showed that injection of propranolol (3 mg/kg) led to a decrease of 31% from the initial level of the heart rate and to a fall in systemic blood pressure (although in some experiments BP was unchanged). The right ventricle was reduced in size (Fig. 1a). This was evidently connected with an increase in the capacity of the vascular bed of the systemic circulation and to a decrease in the venous return, which regularly develops in response to injection of propranolol [1], including in cats [9, 10]. In some experiments the blood flow in the pulmonary vessels was unchanged after injection of propranolol. The blood pressure in the pulmonary artery in the first minute after injection of propranolol rose, but later it fell a little, sometimes down to its original level (Fig. 2a). The increase of pressure in the pulmonary artery was evidently connected with increased activity of the sympathetic nervous system in response to the fall of systemic BP and reduction in ejection of the right ventricle, with predominance of vasoconstrictor α-adrenergic influences following blockade of the β-adrenoreceptors, which have a vasodilator effect on the pulmonary arteries [14]. The resistance of the pulmonary vascular bed increased. The blood flow in the lobar pulmonary artery was reduced or unchanged, whereas the decrease in volume blood flow in the lobar vein was always more marked (Fig. 2a). Obstruction to drainage along the vein and increased resistance of the pulmonary vessels are evidence of elevation of the hydrostatic pressure in the capillaries of the pulmonary circulation, which is accompanied by an increase in the flow rate of lymph in the lungs [12]. Thus injection of propranolol leads to an increase in the inflow of venous blood to the heart, increased hydrostatic pressure in the pulmonary capillaries, and stasis of blood in the lungs.

Injection of NA (0.5 mg/kg) against this background led to a sharp increase of the systemic BP on average by 91% at the 1st minute (Fig. 1b) and an increase of 196% in the pressure in the pulmonary artery by the 3rd minute (Fig. 2b), when signs of acute heart failure were present. This was shown by reduction of the volume velocity of the blood flow in the ascending aorta and conus arteriosus, and arrhythmia. These phenomena were most marked during the first 5-10 min after injection of NA. The blood flow in the lobar pulmonary artery decreased, but the outflow of blood along the lobar vein was reduced even more (Fig. 2b), i.e., retention of blood in the pulmonary system was observed, and was particularly marked by the 10th minute. By this time the system BP had fallen to its initial level or below it. The volume velocity of the blood flow in the pulmonary artery rose a little toward the 7th-10th minute, but remained below its initial level until the end of observation. Despite the reduced inflow of blood into the pulmonary circulation, the drainage along the vein was smaller than the inflow along the artery, i.e., retention of blood continued in the pulmonary circulation until the end of observation (30-65 min). The pulmonary vascular resistance rose by 450% immediately after injection of NA, but later it fell a little, while remaining higher than initially (Fig. 2b).

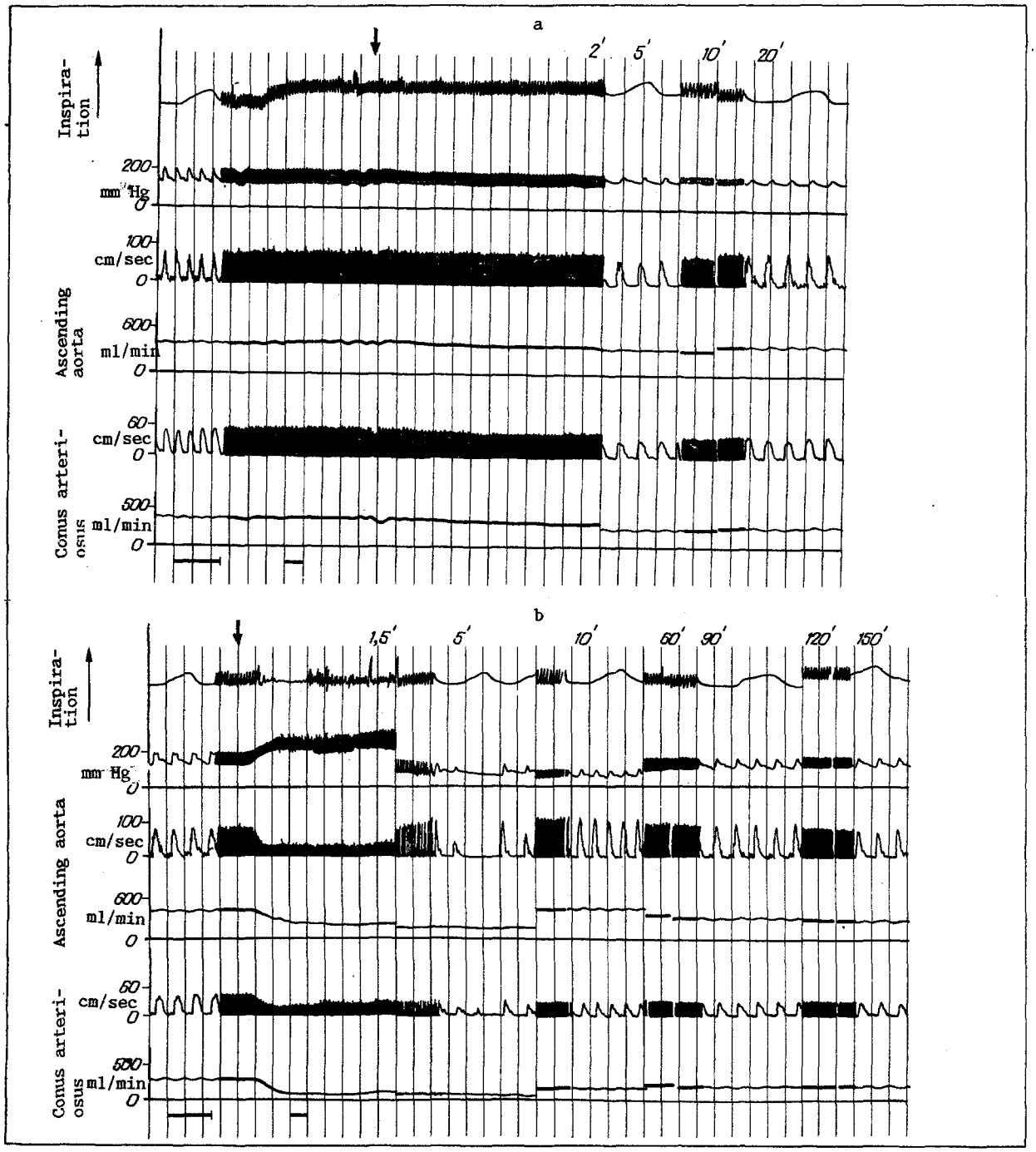

Fig. 1. Changes in cardiac ejection and systemic blood pressure following injection of propranolol (a) and noradrenalin (b). From top to bottom: respiration (pneumogram), blood pressure in femoral artery, phasic blood flow in ascending aorta, mean values of blood flow in ascending aorta, phasic blood flow in conus arteriosus, mean values of blood flow in conus arteriosus. Here and in Fig. 2, thin lines beneath each curve denote zero levels. Arrow indicates time of injection of propranolol (a) or noradrenalin (b). Numbers in top part of figure indicate time (in min) after moment of injection. Time scale: 1 and 10 sec.

Thus injection of NA preceded by propranolol leads to marked disturbances of the hemodynamics, apparently creating the basis for the development of PE. However, the cats under these conditions did not develop PE. This was nothing to do with the general anesthetic, for it did not inhibit the development of noradrenalin-induced PE in albino rats (DR 14.82 ± 0.74). It was shown previously that injection of noradrenalin into albino rats causes a significant increase in permeability of the air—blood barrier for protein molecules [6]. The results indicate that animals of different species differ in their resistance to edemogenic

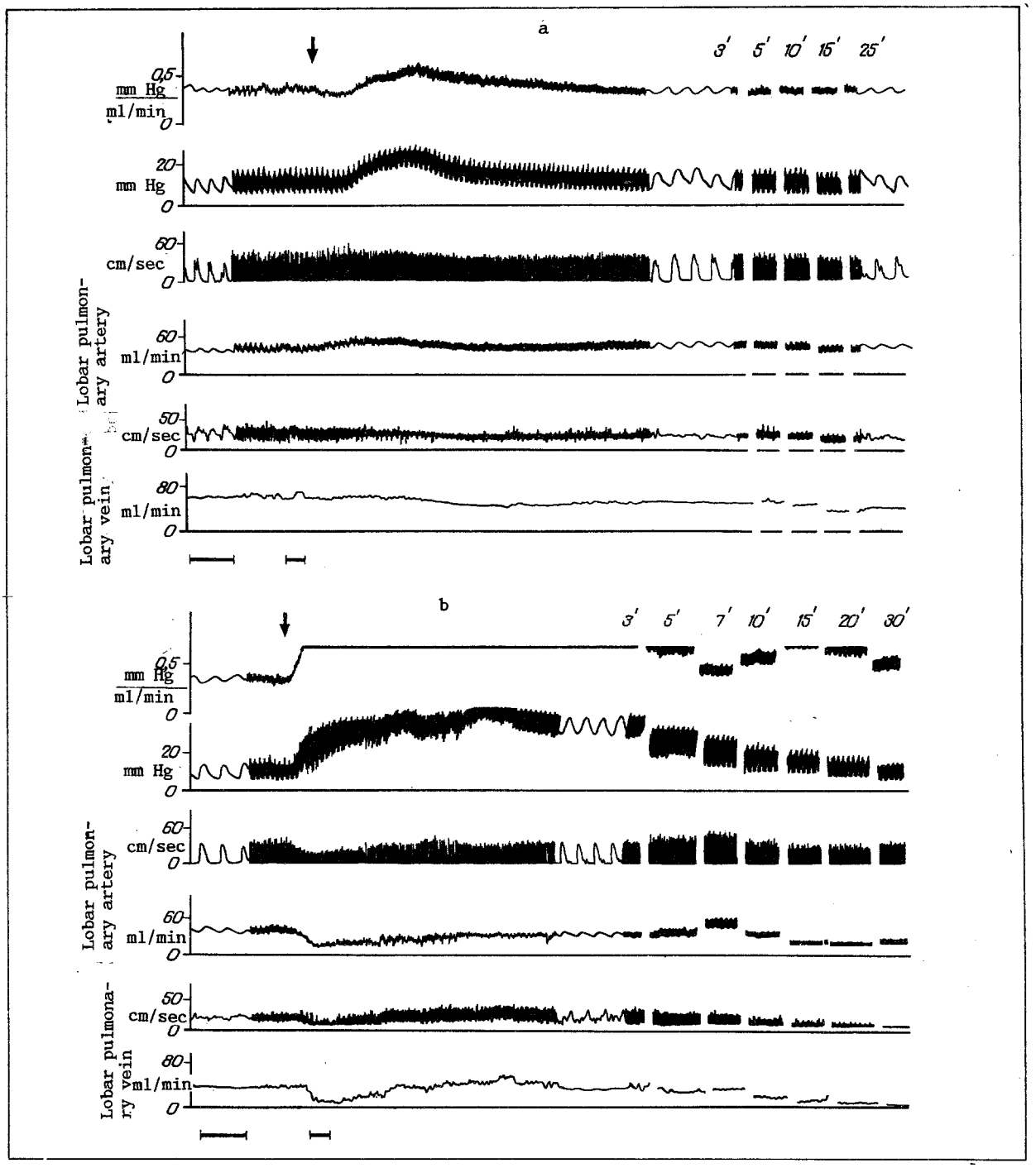

Fig. 2. Changes in parameters of pulmonary hemodynamics after injection of propranolol (a) and noradrenalin (b). From top to bottom: resistance of vascular bed of lower lobe of left lung, blood pressure in pulmonary artery, phasic blood flow in lower lobar pulmonary artery, mean values of blood flow in lower lobar pulmonary artery, phasic blood flow in lower lobar pulmonary vein, mean values of blood flow in lower lobar pulmonary vein. Remainder of legend as to Fig. 1.

agents. In cats, NA evidently does not cause disturbances of vascular permeability in the lungs, and even severe acute disturbances of the hemodynamics do not themselves lead to the development of PE unless pulmonary vascular permeability is increased at the same time. This conclusion is in agreement with data in the literature [7]. However, against the background of altered

(raised) permeability of the air—blood barrier in the lungs, disturbances of the hemodynamics may play a decisive role, leading to a rapid transition from the interstitial form of pulmonary edema to the alveolar form, terminating in rapid death of the animals. Thus injection of propranolol can create a basis for the development of PE. This must be taken into consideration in clinical practice when β-adrenoblockers are prescribed.

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