ACTION OF NORADRENALIN-INDUCED ACTIVATION OF ADRENERGIC STRUCTURES ON HEMODYNAMIC EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$

L. I. Abaskulieva, T. A. Khanumova, and D. M. Velikhanova

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It has been shown that 64% of all prostaglandins (PG) in whole blood are accounted for by PG of the F group, 70% of which consists of $PGF_{2\alpha}$ [15]. This high relative proportion of $PGF_{2\alpha}$ among the other PG groups suggests that it must play an important role in the regulation of the circulatory system. However, this problem has received little study. In particular, much remains to be explained about the effect of PG on hemodynamic parameters such as the systolic ejection and cardiac output (SE and CO respectively) and the total peripheral resistance (TPR) [8, 11, 13, 18].

Considering the complex mutual effects of $PGF_{2\alpha}$ and catecholamines [1, 5] on the activity of the cardiovascular system, it was decided to study the effect of $PGF_{2\alpha}$ on the hemodynamics during activation of the adrenoreceptors of the cardiovascular system by noradrenalin (NA).

EXPERIMENTAL METHOD

Altogether 22 experiments (in three series) were carried out on 15 mature mongrel dogs to study hemodynamic shifts arising in response to intravenous injection of $PGF_{2\alpha}$ in a dose of 3.75 μg/kg (series I), to activation of adrenergic structures by NA in a dose of 0.001 mg/kg (series II), and after injection of $PGF_{2\alpha}$ against the background of adrenoreceptor activation (series III). Premedication with trimeperidine (10 mg/kg, 2% solution) was given and heparin was injected intravenously in a dose of 250 U/kg to prevent the blood from clotting. CO was determined by a fluorometric method, using the Soviet RKÉ-3 apparatus, SE and TPR were calculated by the usual equations, and the venous and arterial pressures and all their components were determined by catheterization of the femoral vessels. The ECG was recorded in standard, amplified, and chest leads, and the heart rate (HR) was determined from the R–R interval and Zuckerman's table. Values of the pressor and cardiac reflexes, their latent period, the maximal amplitude of the response (ΔP_{max}), the maximal rate of change of pressure in the initial phase of the response (ΔV_{max}), the duration of the cardiovascular effect, the character of the aftereffect, the state of myocardial nutrition, and the presence and type of arrhythmia were determined. The results were subjected to statistical analysis [6].

EXPERIMENTAL RESULTS

Administration of $PGF_{2\alpha}$ to the intact animals caused SE to fall by 32.1 ± 4.6% ($p < 0.001$) and CO by 37.8 ± 3.6% ($p < 0.01$), whereas TPR rose by 139.4 ± 11.7% ($p < 0.001$). We know that these shifts are due to the constrictor action of $PGF_{2\alpha}$ on resistive and capacitive vessels, acceleration of outflow, and increased venous return, for both the arterial and venous pressures were observed to rise [4, 5, 10, 12].

This kind of effect of $PGF_{2\alpha}$ was caused both by its direct action on the smooth muscle fibers of the heart and vessels and by its effect through the system of neurohumoral regulators [2, 5, 7, 9, 14].

During activation of adrenoreceptors the action of $PGF_{2\alpha}$ on the hemodynamic parameters was diametrically opposite (Table 1). SE and CO increased, TPR decreased. Only 1 min after

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TABLE 1. Changes in Principal Hemodynamic Parameters under the Influence of $PGF_{2\alpha}$, NA, and of a Combination of Both (M ± m)

Parameter	Series I (control)				Series II	
	initial value	time after injection of $PGF_{2\alpha}$, min			Initial value	Time after injection of Na, min
		1	5	15	1	5
CO	4248,2±335,6	2643,2±287,8	3615,8±306,1	4613,8±356,2	4528,6±421,5	1215,9±196,
	100%	62,2±3,61%	85,1±4,9%	108,6±7,3%	100%	26,5±3,9%
SE	77,4±4,4	53,1±3,0	68,8±2,8	75,1±4,7	68,1±7,6	19,3±4,1
	100%	68,9±4,6%*	87,9±3,3%	97,8±6,5	100%	28,1±6,15
TPR	1589,2±146,7	2215,2±183,5	2185,5±268,7	1633,4±172,9	1453,8±147,0	10009,9±887,
	100%	139,4±11,7%	137,5±19,8%	102,8±13,4%	100%	687,8±61,0%*
Pressure:						
systolic	104,5±3,5	118,2±7,1	120,3±3,1	109,5±2,5	99,2±4,1	162,0±7,2
	100%	113,4±5,7%	155,5±3,8%*	104,3±6,1%	100%	163,6±7,1%*
diastolic	69,0±5,1	86,3±8,5	83,1±5,6	72,3±4,6	74,6±5,3	147,1±14,3
	100%	125,0±9,4%	120,4±4,6%	104,9±7,7%	100%	197,4±19,2%*

Parameter	Control		Series III			
	time after injection of NA, min		initial value	time after injection of $PGF_{2\gamma}$ preceded by Na, min		
	5	15		1	5	15
CO	4865,0±404,6	4469,7±418,2	1128,5±201,0	1624,4±148,9	3839,8±194,2	3878,0±140,2
	107,0±8,9%	98,1±4,5%	100%	143,9±13,2%	340,2±17,2%*	343,6±12,4%*
SE	69,5±6,2	63,4±3,5	18,5±2,8	26,2±2,0	52,6±2,0	55,4±3,1
	102,2±9,1%	93,2±5,2%	100%	141,6±11,0%*	284,0±18,1%*	299,4±16,8%*
TPR	1276,0±126,1	1473,1±134,8	11030,5±1905,0	7091,8±820,0	2012,6±223,35	1889,0±276,0
	88,0±8,7%	101,1±6,7%	100%	64,3±7,4%	18,3±2,0%*	17,0±3,4%*
Pressure:						
systolic	93,4±2,9	95,6±6,6	167,0±6,6	156,2±9,7	108,9±8,7	100,3±5,6
	93,9±2,9	95,9±6,6%	100%	93,4±5,8%	65,2±5,1%*	59,0±3,2%*
diastolic	70,8±3,1	76,2±5,5	150,1±6,5	138,3±4,8	90,7±7,1	86,4±5,5
	94,5±4,2	102±9,5%	100%	9261±3,2%	60,3±4,6%*	57,5±3,5%*

*Footnote missing from Russian original — Publisher.

injection of $PGF_{2\alpha}$ SE was increased by 41.6 ± 11.0% ($p < 0.05$) and CO by 43.9 ± 13.2% ($p < 0.01$), whereas TPR was reduced by 35.7 ± 7.4% ($p < 0.1$). After 5 min the action of $PGF_{2\alpha}$ was similar but much greater: SE and CO were increased by 184.0 ± 18.1% ($p < 0.001$) and 240.2 ± 17.2% ($p < 0.001$) respectively and TPR was reduced by 81.7 ± 2.0% ($p < 0.001$). After 15 min the effect of $PGF_{2\alpha}$ reached its maximum: SE was increased by 199.4 ± 16.8% ($p < 0.001$), CL by 243.6 ± 12.4% ($p < 0.001$), and TPR was reduced by 83.0 ± 3.4% ($p < 0.001$). The same pattern was maintained during the next 30 min.

Unlike the effects on the animals of series I, in dogs with adrenoreceptor activation a depressor response was observed after injection of $PGF_{2\alpha}$. Under these circumstances the arterial pressure (BP) fell but HR increased.

Similar results have been obtained in experiments on anesthetized male rats receiving larger doses of $PGF_{2\alpha}$ [3]. It has also been shown that the pressor response to $PGF_{2\alpha}$ was much weaker in rats with a model of renovascular hypertension and also in spontaneously hypertensive rats than in normotensive animals [4].

The paradoxical hemodynamic response of $PGF_{2\alpha}$ against the background of the action of NA is connected with a readjustment of hemodynamic homeostasis, expressed as constriction of the resistive and capacitive vessels, elevation of both arterial and venous pressure, an increase in TPR (by 587.8 ± 61.0%, $p < 0.001$), and by a decrease in SE (by 71.9 ± 6.1%, $p < 0.001$) and CO (by 73.5 ± 3.9%, $p < 0.001$). Under these circumstances the baroreflex impulsation is increased, leading to a depressor aftereffect of NA.

$PGF_{2\alpha}$, if injected at the peak of the pressor response to NA, abolished the depressor aftereffect of the latter (possibly due to the selective effect of $PGF_{2\alpha}$ on the vasomotor center of the medulla [16, 20], and abolished the negative chronotropic reaction and disturbances of the cardiac rhythm, induced by it, in the form of arrhythmia, atrioventricular block of the I–II degree, and single ventricular extrasystoles. The duration of the pressor effect was lengthened and the positive chronotropic action of NA increased. As a result cardiac activity was improved, SE and CO increased, and vasoconstriction and TPR were reduced.

There are indications that PG of the F group increase acetylcholine production and lead to release of NA from adrenergic nerve endings. It can be tentatively suggested that $PGF_{2\alpha}$, if injected after NA, cannot realize its own constrictor effect because of the increase in acetylcholine production, leading to activation of muscarinic and nicotinic cholinergic structures and corresponding hemodynamic shifts, in the form of slowing of the heart, reduction of TPR, vasodilatation, and a fall of blood pressure. Meanwhile, transmission from preganglionic to postganglionic fibers is probably facilitated and the central time of the reflexes reduced, as is shown by shortening of the latent period of the pressor reflex from 26.0 ± 1.8 sec in the control to 20.0 ± 1.6 sec ($p < 0.05$) in the experiment in the present investigation.

Injection of NA is known to stimulate synthesis and accumulation of PG of the F group. Thus the $PGF_{2\alpha}$ concentration may be increased on account of endogenous $PGF_{2\alpha}$ synthesized and released from the vessel wall [10]. As a result, acetylcholine production is increased, with all the consequent hemodynamic shifts: an increase in SE and CO, a decrease in TPR, vasodilatation, reduction of the amplitude of the pressor reflex, and improvement of the condition of the microcirculatory system.

LITERATURE CITED

1. A. G. Aivazyan, "Prostaglandins E and F under conditions of adrenoreceptor excitation, hypoxia, and cerebral ischemia," Author's Abstract of Dissertation for the Degree of Candidate of Medical Sciences, Erevan (1980).
2. R. G. Boroyan, "Cardiovascular effects of prostaglandins and data on the mechanisms of their action," Author's Abstract of Dissertation for the Degree of Doctor of Medical Sciences, Erevan (1979).
3. Sh. I. Ismailov and L. A. Serebryakov, Farmakol. Toksikol., No. 5, 576 (1975).
4. Sh. I. Ismailov and A. V. Val'dman, Byull. Éksp. Biol. Med., No. 8, 45 (1982).
5. Kh. M. Markov, A. V. Kozlov, and V. G. Pinelis, Kardiologiya, No. 3, 75 (1981).
6. E. V. Montsevichyute-Éringene, Patol. Fiziol., No. 4, 71 (1964).
7. V. D. Pomoinetskii, Ter. Arkh., No. 6, 141 (1980).
8. V. V. Ryazhenov and A. N. Kudrin, Farmakol. Toksikol., No. 1, 50 (1975).
9. Z. A. Suslina, N. V. Lebedeva, and V. P. Zykova, Zh. Nevropatol. Psikhiat., No. 7, 948 (1979).
10. E. V. Flerov and Sh. I. Ismailov, Farmakol. Toksikol., No. 1, 44 (1977).
11. J. M. Armstrong and A. L. A. Boura, International Conference on Prostaglandins, Florence (1975), p. 124.
12. D. W. Du Charme, J. R. Weeks, and R. G. Montgomery, J. Pharmacol. Exp. Ther., 160, 1 (1968).
13. P. Even, F. Dray, and H. Sors, International Conference on Prostaglandins, Florence (1975), p. 126.
14. L. Favre and M. B. Valloton, Schweiz. Med. Wochenschr., 113, 1042 (1983).
15. M. Greaves and W. McDonald-Gibson, Br. Med. J., 2, 83 (1972).