Arterial Pressure Lability in Hypotensive Effects of Clonidine in Barodenervated Spontaneously Hypertensive Rats

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Hypotensive effect of clonidine and its effect on arterial pressure lability as the main index of stability of background blood pressure are studied in intact spontaneously hypertensive rats (SHR) and rats with chronic sinoaortic denervation. Barodenervation potentiates hypotensive and negative cardiochronotropic effects of clonidine, which is accompanied by reduced blood pressure lability. This indicates an increased sensitivity of central α_2- and imidazoline receptors, which mediate the depressor effect of clonidine, against the background of chronic inhibition of the baroreceptor reflex.

Key Words: *lability; clonidine; sinoaortic barodenervation*

Arterial pressure lability (APL), i.e., the range of spontaneous fluctuation of its mean level, is an important index of stability of the baseline arterial pressure (AP). Regulation of APL certainly plays a leading role in AP normalization in various pathologies associated with disturbed regulation of the cardiovascular system. These disturbances affect tonic afferentation from baroreceptors modulating the sensitivity of central imidazoline and α-adrenoreceptor, which mediate the effect of central hypotensive preparations of the clonidine family [1,5]. However, analysis of hypotensive effect of these preparations usually ignores their effect on APL in conscious animals both in health and under conditions of chonically disturbed baroreflex. The latter can be experimentally modeled by sinoaortic barodenervation (BD).

The aim of the present study was to evaluate hypotensive effect of clonidine and its effect on APL in conscious spontaneously hypertensive animals in health and under conditions of sinoaortic deafferentation.

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MATERIALS AND METHODS

Experiments were carried out on conscious male SHR weighing 250-300 g with intact or chronically denervated baroreceptors. One day before the experiment the rats were narcotized with Nembutal (40 mg/kg, intraperitoneally), and PE10 polyethylene catheters (Clay Adams) were inserted through the femoral artery into the aorta for AP monitoring and into the jugular vein for drug infusion. Peripheral ends of the catheters were fixed between the scapulae.

Barodenervation was performed as described previously [8] by cutting the laryngeal nerve near its junction with the vagus nerve and excision of the superior cervical ganglion including a small preganglionic fragment (4-5 mm) of the cervical sympathetic trunk. For denervation of the carotid sinus all adjacent nerve fibers were removed, and the internal, external, and common carotid arteries were treated with 5% phenol. The experiments were performed 7-10 days postoperation.

Barodenervation was verified by the degree of bradycardia in response to elevation of mean AP induced by intravenous injection of phenylephrine

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(3 μg/kg). The animals whose heart rate in response to AP rise by 40 mm Hg decreased by no more than 20 beats/min were regarded as barodenervated and used in further experiments.

The studied parameters were recorded every second for 40 min on an IBM PC/AT computer using a Lability software developed at the Department of Pharmacology, Faculty of Fundamental Medicine, Moscow State University. Bearing in mind that BD markedly increases APL, which hampers precise determination of its mean level, mean AP before and after infusion of clonidine were calculated as the means for the corresponding 5-min intervals.

Arterial pressure lability was calculated as the mean deviation from the mean AP [2,6]; the significance of intergroup differences was assessed using the Student test.

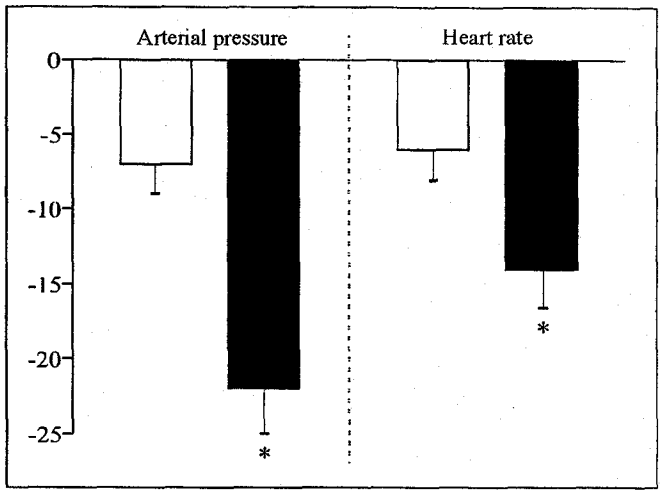

Fig. 1. Effect of chronic barodenervation on hypotensive and negative chronotropic effects of clonidine (5 μg/kg) in conscious SHR. Open bars: control rats; dark bars: barodenervated rats; *$p<0.05$ compared with the control. Ordinate: percent of the control level.

RESULTS

Data presented in Table 1 suggest that sinoaortic barodenervation has no effect on the baseline AP, although it induces tachycardia in conscious SHR ($p<0.05$).

Intravenous injection of clonidine (5 μg/kg) to control animals led to a significant decrease in the mean AP and heart rate by 14±3 mm Hg and 18±5 beats/min from the initial level, respectively. Injection of the same dose of clonidine to BD rats induced a more pronounced hypotension and bradycardia (by 40±9 mm Hg and 44±14 beats/min, respectively, Fig. 1). Maximum shifts in the hemodynamic parameters were noted between 15 and 25 min postinjection.

Potentiation of the hypotensive effect mediated via stimulation of the central α_2- and imidazoline receptors against the background of BD has been previously shown on normotensive animals [4,9]. However, in normotensive rats with intact baroafferents injection of 5 μg/kg clonidine did not induce any significant decrease in AP [9,10]. It can be assumed that central imidazoline- and α-adrenoreceptors in conscious spontaneously hypertensive rats are more sensitive to drugs of the clonidine family. Moreover, it has been shown that baroreflex sensitivity in intact SHR is considerably reduced in comparison with normotensive rats [3,7].

Barodenervation considerably elevated APL ($p<0.05$) and had no effect on the baseline AP (Table 1). Clonidine significantly reduced APL ($p<0.05$) only in BD rats (by 42±16% of the initial value). Lability of the heart rate was practically the same in barodeafferentated and control animals.

The observed decrease in APL induced by clonidine against the background of BD suggests that the development of the hypotensive effect of clonidine is accompanied by directed stabilization of the baseline AP.

Thus, BD in conscious spontaneously hypertensive rats potentiates hypotensive and negative cardiochronotropic effects of clonidine. The effect of clonidine is accompanied by a decrease in APL, which attests to sensitization of central imidazoline- and α-adrenoreceptors mediating the depressor effect of clonidine against the background of chronic sinoaortic barodenervation. These data suggest that these hypotensive preparations can be successfully used in various states characterized by suppression of baroreflex (stress, chronic heart failure, and acute pain syndrome).

TABLE 1. Effect of Clonidine (5 μg/kg) on AP, Heart Rate, and Their Lability in Barodenervated SHR (*M*±*m*)

Group	Mean AP, mm Hg		Heart rate, beats/min		APL, mm Hg		Lability of heart rate, beats/min	
	background	clonidine	background	clonidine	background	clonidine	background	clonidine
Control rats (n=8)	199±5	185±6*	331±13	312±14	3.8±0.6	4.7±0.6	10.8±0.8	9.7±1.0
BD rats (n=6)	185±6	145±13*	404±24**	360±22	6.7±1.2**	3.9±1.0*	12.0±1.1	12.9±3.4

Note. $p<0.05$: *compared with the baseline values; **compared with the control; n: number of experiments.

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