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Opposition of Rapid Baroreceptor Resetting by Prostanoids in Rabbits

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Abstract

Arterial baroreceptors reset rapidly within minutes during acute hypertension; baroreceptor pressure threshold (Pth) is increased and the pressure-baroreceptor activity relation is shifted to the right. The purpose of the present study was to determine if prostacyclin (PGI_2) or other prostanoids released during acute hypertension modulate the magnitude of baroreceptor resetting. Baroreceptor activity was recorded from the vascularly-isolated carotid sinus during distension of the sinus with slow pressure ramp in rabbits anesthetized with chloralose. Pressure-activity curves were generated after holding carotid sinus pressure for 10-15 min from 30 to 100 mmHg. In control, the elevation of holding pressure increased Pth from 44± to 65±5 mmHg ($p < 0.05$, $n = 12$). In the presence of PGI_2 (20 μM), Pth averaged 43±4 and 45±3 mmHg ($n = 12$) after holding pressure at 30 and 100 mmHg, respectively. In the control group before exposing the carotid sinus to indomethacin, an elevation of holding pressure increased Pth from 49±2 to 71±3 mmHg ($p < 0.05$, $n = 12$). After inhibition of the endogenous formation of prostanoids with indomethacin (20 μM), Pth increased by a significantly greater extent from 61±2 to 90±3 mmHg ($p < 0.05$, $n = 12$) with the increase in holding pressure. The slope of the pressure-activity curve (baroreceptor gain) was not infuenced by the change in holding pressure. It was increased significantly by PGI_2, while decreased by indomethacin. Neither the change in holding pressure nor PGI_2 affected the circumferential wall strain of carotid sinus over a wide range of pressure alteration. The results suggest that PGI_2 or other prostanoids released during acute hypertension sensitizes baroreceptors and provides a negative feedback mechanism that opposes and limits the magnitude of rapid baroreceptor resetting.

Key Words: acute hypertension, endothelium, prostaglandins, rapid baroreflex resetting

Introduction

In chronic hypertension, arterial baroreceptors are reset and function around a higher set point of pressure (1, 2, 22). It has been established that resetting of arterial baroreceptors does not necessarily require a long duration of pressure elevation. An increase in the pressure threshold (Pth) of baroreceptors and a shift to the right of the pressure-discharge relationship can occur within minutes following an acute increase in pressure (2, 3, 8, 11, 14-16, 25). Previous studies from our laboratory have also demonstrated that acute resetting of the baroreflex control on the arterial pressure and vascular resistance (5, 6).

The mechanism of rapid baroreceptor resetting is still not known. Several theories have been proposed including viscoelastic creep of vessel wall elements coupled in series with baroreceptors (9, 19) and ionic mechanisms such as activation of Na^+, K^+-ATPase which may lead to membrane hyperpolarization and decreased baroreceptor activity after a period of acute hypertension (14-16, 29).

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Previous investigations have revealed that prostanoids released from vascular endothelium, act in a paracrine manner to increase baroreceptor sensitivity (7, 23, 31). Acute hypertension and increased vascular stretch enhance the formation of prostanoids in blood vessels (17, 18). Therefore, we hypothesized that prostanoids released during an acute increase in arterial pressure should promote increased barorecept or sensitivity and oppose rapid baroreceptor resetting. To test this hypothesis we have determined the magnitude of carotid sinus baroreceptor rapid resetting in response to a short-term increase in carotid sinus pressure during: 1) control; 2) exposure of the isolated carotid sinus to prostacyclin (PGI_2); and 3) after inhibition of endogenous formation of pro-stanoids with intrasinus administration of indo-methacin.

Material and Methods

Male white rabbits of New Zealand strain were used. The animals were anesthetized with α-chloralose (80-90 mg/kg) injected through the marginal ear vein. Supplemental doses (10 mg/kg) were given as needed. The trachea was cannulated to provide artificial ventilation with a mixture of oxygen and room air (tidal volume 10-12 ml and respiratory rate 40-60 per min). The femoral artery and vein were catheterized for recording of arterial blood pressure and administration of anesthetics, respectively. Body temperature was maintained at 37-38°C by external heating. Before nerve recording, the animal was paralyzed with decamethonium bromide (2 mg/kg, i.v.) to avoid muscular movement. A polygraph recorder (Gould 2800S) was used to monitor all the recordings.

Isolated Carotid Sinus Preparation

The carotid sinus on one side was vascularly isolated according to the methods described previously (6, 23). It was accomplished by ligating the thyroid, internal carotid, occipital and lingual arteries as well as other small branches from the sinus region. The vagus and aortic nerves on the same side of the carotid sinus were severed. After identification of the carotid sinus nerve, all nerves other than the sinus nerve were tied or cut to eliminate possible effects of sympathetic innervation to the sinus. Carotid sinus pressure was measured through a cannula (PE50) in the external carotid artery connected to a Statham transducer. A catheter (PE90) was inserted into the common carotid artery until its tip reached a level approximately 1.5 mm below the sinus region. The catheter was connected to a reservoir filled with physiologic saline solution of the following composition (in mM): NaCl 98.0, KCl 4.7, $NaHCO_3$ 24.0, KH_2PO_4 1.1, $MgSO_4$ 1.2, $CH_3COONa{\cdot}3H_2O$ 20.0, $CaCl_2{\cdot}2H_2O$ 2.5, Glucose 10.0. Before the experiment, the saline solution was warmed to 37°C by a temperature-controlled water jacket. The isolated sinus was periodically refilled with oxygenated solution.

Nonpulsatile carotid sinus pressure was altered by a pressure regulating system connected to the reservoir. An air-filled syringe was used to produce step changes in pressure. Slow ramp increases in pressure were achieved by adjusting a gas regulator valve connected to a pressurized air source.

Recording of Carotid Sinus Nerve Activity

The carotid sinus nerve was isolated and sectioned at its junction with the glossopharyngeal nerve. The nerve was placed on a platinum unipolar electrode and encased in silicone gel (Wacker Silicones Corp., Adrian, MI). At least 30 min were allowed for the silicone gel to harden. Care was taken not to cover the internal carotid artery and sinus region with the gel. Throughout the experiment, the isolated carotid sinus was bathed externally with physiological saline to avoid drying.

Nerve activity was recorded with a Grass probe (Model HIP511E, Grass Instrument Co., Quincy, MA) and a Tekronix band-pass amplifier Model P555). The high-frequency cutoff was set at 1000-3000 Hz and low-frequency cutoff at 30 Hz. The amplifier output was led to a loudspeaker and a dual-beam storage oscilloscope (Model D13, Tektronix, Beaverton, OR). A nerve traffic analyzer (Model 706C, University of Iowa Bioengineering, Iowa City) was used to quantify baroreceptor activity. Since the absolute value of whole nerve activity depends on the number of active fibers in contact with the recording electrode and may vary between preparations, nerve activity is expressed as a percentage of the maximum activity recorded during the initial pressure ramp from 0 to 175 mmHg.

Carotid Sinus Diameter and Strain

We used a sonomicrometer system to measure changes in carotid sinus diameter (7, 15, 30). In brief, two miniature piezoelectric crystals (5 mHz) attached to a low resistance stainless steel clip were placed on either side of the carotid sinus. The clip was secured by suturing it to the adventitia. Vessel diameter was determined from the transit time of the acoustic signals between the crystals. Preliminary tests indicated that the acoustic signals was occasionally unstable at pressures below 50 mmHg. Therefore, pressure was initially held at 50 mmHg when measurements of carotid sinus diameter were obtained. Circumferential wall strain between pressures of 50, 100, and 150

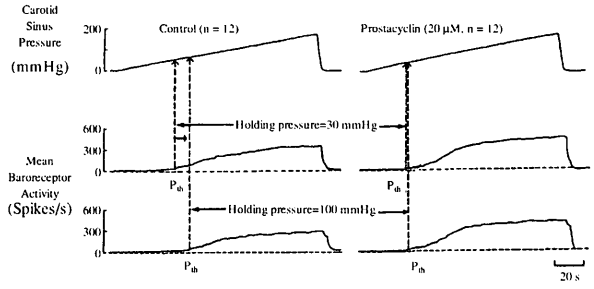

Fig. 1. Original recordings of increases in mean baroreceptor activity in response to ramp increases in carotid sinus pressure during control (left panel) and during exposure of the carotid sinus to prostaglandin (20 μM; right panel). An increase in holding pressure from 30 to 100 mmHg reset baroreceptor Pth and the pressure-activity relation was shifted to the right in the control condition. In contrast, prostacyclin increased baroreceptor sensitivity and abolished the resetting. Pressure ramps were essentially superimposable after each level of holding pressure.

mmHg was calculated as: (D-Do)/Do where D = diameter and Do = initial diameter at a low pressure of 50 mmHg.

Drugs

PGI_2 (Sigma) was dissolved in cold sodium bicarbonate solution (1 mM, pH 9-10). Aliquots were prepared in plastic tubes and lyophilized with a freeze dryer (20 μg PGI_2/tube). Aliquots containing PGI_2 were diluted into physiologic saline solution to make appropriate concentrations immediately before use. Indomethacin (Sigma) was dissolved in physiologic saline solution with sodium carbonate (3:1 ratio) to increase solubility. For each drug, vehicle solutions were prepared for control injections.

Protocols

The effects of PGI_2 and indomethacin on rapid baroreceptor resetting were investigated in anesthetized rabbits. Carotid sinus pressure was initially held at 30 mmHg for 10-15 min. Pressure was then rapidly decreased to 0 mmHg and slowly elevated in a ramp fashion (less than 5 mmHg/sec) to 175 mmHg (Fig. 1). The rate of increase in pressure was constant for repeated trials within each experiment. Rapid baroreceptor resetting was produced by increasing the holding pressure from 30 mmHg to a level of 100 mmHg (+70 mmHg) for 10-15 min. Pressure was then rapidly decreased to 0 mmHg and the pressure ramp repeated. The same procedures were performed during exposure of the carotid sinus to PGI_2 (20 μM) and to indomethacin (20 μM). Because PGI_2 has short duration of action and is chemically unstable, the solution containing this agent was placed inside and outside the sinus region 30 sec to 1 min before measuring the baroreceptor response to the pressure ramp. The saline solution originally placed outside the sinus region was removed with suction and replaced by the solution containing PGI_2. Indomethacin was placed in the isolated carotid sinus at pressures of 30 and 100 mmHg 10 min before the pressure ramp was applied.

The influences of increased holding pressure and exposure of the sinus to PGI_2 on circumferential strain of the carotid sinus were determined in separate experiments (n = 6). Changes in diameter in response to a ramp increase in pressure were measured after holding pressure at 50 mmHg and after increasing pressure by 70 mmHg to a value of 120 mmHg for 10-15 min. Vehicle and PGI_2 were placed inside and outside the carotid sinus 30 sec to 1 min before the ramp increases in pressure were applied.

Data Analysis

Measurements of baroreceptor activity were expressed as a percentage of maximal activity recorded during the control ramp and plotted as a function of changes in carotid sinus pressure. Baroreceptor pressure threshold (Pth) which the level of pressure during the ramp that nerve activity begin to increase in a continuous manner from baseline. The value was obtained according to a method developed by Chen and Chang (4). The slope of the linear portion of the pressure-activity curve from Pth to 150 mmHg (baroreceptor gain) was calculated by regression analysis. Carotid sinus wall strain (d-do/do) was measured and calculated at pressures of 100 and 150 mmHg.

The influences of the change in holding pressure, exposure to PGI_2 and indomethacin on baroreceptor Pth, baroreceptor gain, and circumferential wall strain were analyzed by paired *t* test (30). Differences were considered significant at $p < 0.05$.

Results

An increase in the holding carotid sinus pressure caused rapid baroreceptor resetting; Pth increased and the pressure-activity curve shifted to the right (Figs. 1 and 2). Exposure of the isolated carotid sinus to PGI_2 (20 μM, n = 12) did not influence Pth after holding pressure at 30 mmHg but significantly decreased Pth after holding pressure at 100 mmHg (Fig. 3). Thus, rapid resetting of Pth to higher levels in response to increased holding pressure was abolished in the presence of PGI_2 (Fig. 3). Prevention of resetting was also evident by the absence of a significant shift in the overall pressure-activity curve with increased holding pressure in the presence of PGI_2 (Fig. 2).

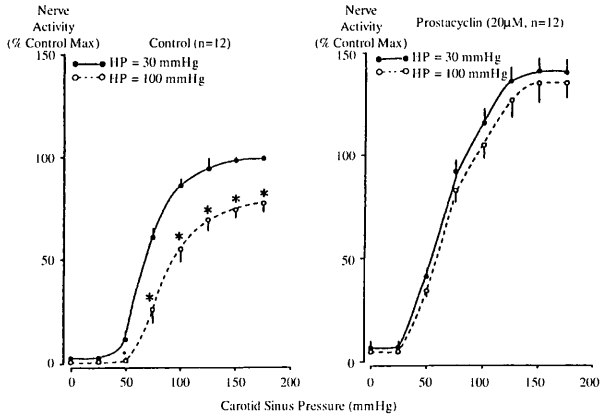

Fig. 2. Influence of prostacyclin (20 μM, n = 12) on baroreceptor pressure-activity curve and rapid resetting. Left Panel: Rapid resetting of pressure-activity curve in the control condition. Increasing holding pressure from 30 to 100 mmHg for 10-15 min significantly reset the baroreceptor function curve to the right. Right Panel: Exposure of the isolated carotid sinus to prostacyclin (20 μM) increased the slope of the pressure-activity curve, elevated maximum baroreceptor activity, while abolished rapid resetting. Values are means±SEM. *p < 0.05, significant difference vs. HP = 30 mmHg group.

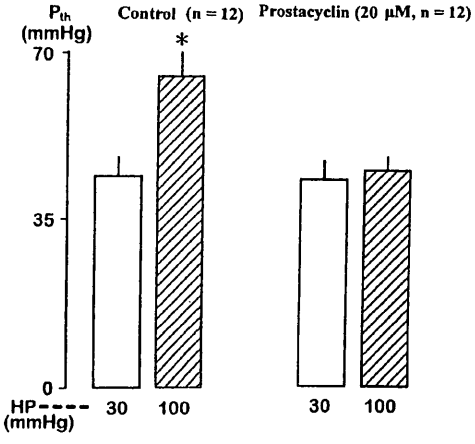

Fig. 3. Rapid resetting of baroreceptor Pth during control and prostacyclin (20 μM, n = 12). In the control group, Pth increased significantly (*p < 0.05) after an elevation in holding pressure (HP) from 30 to 100 mmHg. In contrast, under the exposure of the isolated carotid sinus to prostacyclin did not significantly affect the Pth by the increase in holding pressure.

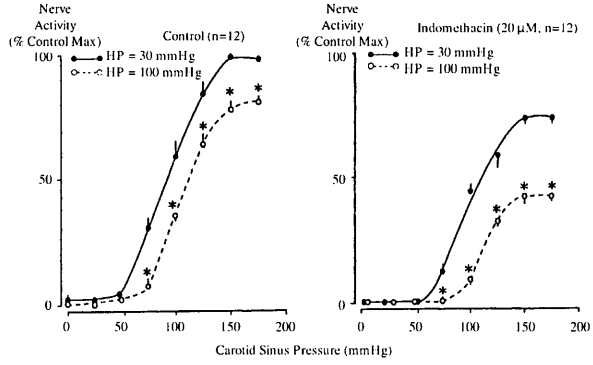

Fig. 4. Influence of indomethacin (20 μM, n = 12) on baroreceptor pressure-activity curve and rapid resetting. Left Panel: Rapid resetting of pressure-activity curve in the control condition (HP, holding pressure). Right Panel: Exposure of the isolated carotid sinus to indomethacin decreased baroreceptor activity and augmented the shift of the pressure-activity curve to the right after the increase in holding pressure. Values are means±SEM. *p < 0.05, significant difference vs. HP = 30 mmHg group.

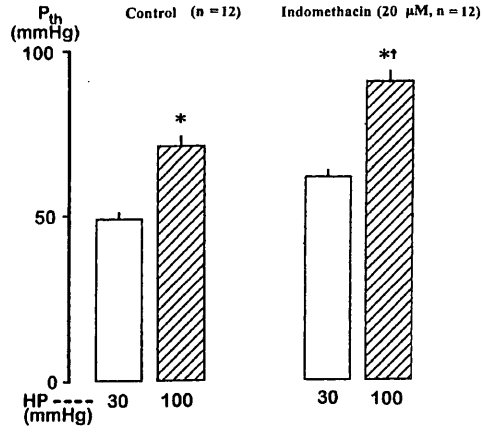

Fig. 5. Rapid resetting of baroreceptor Pth during control and indomethacin (20 μM, n = 12). During control, Pth increased significantly (*p < 0.05) after increasing the holding pressure (HP) from 30 to 100 mmHg. Indomethacin enhanced the increase in Pth in response to elevated holding pressure. * indicates significant increase in Pth with increased holding pressure and † indicates significant increase in Pth with elevated HP in presence of indomethacin compared with control, p < 0.05.

Exposure of the isolated carotid sinus to the cyclooxygenase inhibitor indomethacin (20 μM, n = 12) increased Pth significantly and augmented resetting of the Pth to higher levels in response to the rise in holding pressure (Figs. 4 and 5). Before indomethacin, Pth increased from 49±2 to 71±3 mmHg (+22±2 mmHg) in response to increased holding pressure. After inhibition of endogenous formation of prostanoids with indomethacin, Pth increased to a significantly greater extent from 61±2 to 90±3 mmHg (+29±2 mmHg) with the rise in holding pressure (Fig. 5). The enhancement of rapid baroreceptor resetting by indomethacin was even more evident by more significant shift in the overall pressure-activity curve with increased holding pressure in the presence of indomethacin (Fig. 4).

The slope of the baroreceptor pressure-activity curve (baroreceptor gain) was not influenced by the change in holding pressure (Table 1). PGI_2 increased and indomethacin decreased baroreceptor gain significantly (Table 1).

Neither the increase in holding pressure nor exposure of the carotid sinus to PGI_2 significantly influenced circumferential wall strain calculated at pressures of 100 and 150 mmHg (Table 2).

Table 1. Influences of Prostacyclin, Indomethacin, and Holding Pressure on the Slope of the Baroreceptor Pressure-Activity Relation

	Baroreceptor slope (%/mmHg)			
	Control	Prostacyclin	Control	Indomethacin
Holding pressure = 30 mmHg	0.87±0.05	1.12±0.08*	0.94±0.03	0.83±0.2*
Holding pressure = 100 mmHg	0.88±0.03	1.13±0.09*	0.97±0.06	0.75±0.03*

Values are means±SEM (n = 12 for each group). *$p < 0.05$, significant difference between control and the corresponding treated group.

Table 2. Lack of Influence of Holding Pressure and Prostacyclin on Circumferential Wall Strain of the Carotid Sinus

Holding pressure	Wall strain at 100 mmHg		Wall strain at 150 mmHg	
(mmHg)	Control	Prostacyclin	Control	Prostacyclin
50	0.31±0.01	0.29±0.01	0.52±0.03	0.52±0.03
120	0.34±0.02	0.32±0.02	0.53±0.02	0.54±0.03

Values represent means ± SEM (n = 6).

Discussion

The results confirm previous studies that demonstrated sensitization of baroreceptors by PGI_2 and decreased baroreceptor sensitivity after inhibition of endogenous prostanoid formation with indomethacin (7, 23, 31). The major new findings are that rapid baroreceptor resetting during acute increases in arterial pressure is attenuated by PGI_2 but augmented by indomethacin. The results suggest that PGI_2 or other prostanoids released during acute hypertension oppose rapid baroreceptor resetting.

In agreement with previous studies (2, 3, 5, 6, 8, 9, 11, 14-16, 19, 25), rapid baroreceptor resetting in our experiments was characterized by a shift in Pth in the direction of the change in holding pressure without a change in the slope of the pressure-activity curve. We also found that increasing the carotid sinus holding pressure from 30 to 100 mmHg decreased the maximum plateau level of baroreceptor activity to a significant extent (Figs. 1, 2 and 4). Although maximum activity was not influenced by rapid baroreceptor resetting in the majority of previous studies (8, 9, 11, 24), Yao and Thoren (33) in agreement with our results, found decreased maximum activity of rabbit carotid sinus baroreceptors after a 30 min period of increased carotid sinus pressure.

Several mechanisms have been proposed to mediate rapid baroreceptor resetting including activation of an electrogenic Na^+ pump (14, 28) and viscoelastic relaxation or creep of elements of the vessel wall coupled in series with baroreceptor nerve endings (9, 18). Our study was not designed to explore the role of these mechanisms in resetting. Nevertheless, we found no evidence of viscoelastic creep based on measurement of the carotid sinus pressure-diameter relation before and after changes in holding pressure. The viscoelastic hypothesis predicts that gradual relaxation and lengthening of the viscoelastic element during the period of increased pressure would result in an upward shift in the pressure-diameter curve with increased diameter at a given pressure after the period of acute hypertension. In our experiments, the pressure-diameter curve and calculated wall strain were not influenced significantly by the change in holding pressure (Table 2). Others have also found a dissociation between rapid baroreceptor resetting and viscoelastic changes in the vascular pressure-diameter relationship (15, 25).

Regardless of the mechanism of rapid baroreceptor resetting, the present results suggest that the magnitude of rapid resetting can be modulated to a significant extent and that vascular prostanoids oppose resetting. The vascular endothelium is the major source of prostanoids produced in the vessel wall (23). Endothelial denudation of the carotid sinus decreases baroreceptor sensitivity and sensitivity is restored by addition of PGI_2 to the denuded sinus (7) suggesting that the endothelium is an important source of prostanoids that modulate baroreceptor function.

Furthermore, endothelial cells possess ion channels responsive to mechanical stretch (19) and increased stretch enhances prostanoid formation (16, 17). Thus, prostanoids released during vascular stretch may act in a negative feedback manner to limit the extent of baroreceptor resetting during acute hypertension. Previous studies have also provided evidence that rapid baroreceptor resetting is not only a function of the magnitude of the change in mean pressure but can be modulated selectively by various factors including pulse pressure (3) and drugs used to treat hypertension (10, 27).

Modulation of rapid baroreceptor resetting by prostanoids such as PGI_2 may have important clinical implications. Rapid resetting during acute hypertension enables the arterial pressure setpoint to remain on the steep portion of the pressure-activity curve and therefore preserves the ability to detect rapid fluctuations in pressure around the new higher level of pressure. The potential disadvantage is that the decline in baroreceptor activity promotes a reflex increase in sympathetic discharge and maintenance of the elevated pressure. Thus, the capacity to restore a "normal" absolute level of blood pressure is reduced by rapid baroreceptor resetting. By preventing excessive resetting during acute hypertension, PGI_2 may enhance the ability to normalize the absolute level of pressure. The sensitivity to rapid fluctuations in pressure may be relatively preserved by the marked increases in baroreceptor slope and maximum activity caused by PGI_2 (see Fig. 2)

Pathologic states such as atherosclerosis and chronic hypertension are associated with impaired function of endothelium and decreased PGI_2 formation (12, 13, 20, 26). Results of previous studies (30, 32) suggest that the impaired formation of prostanoids contributes to the chronic baroreceptor resetting that is evident in these diseases.

A previous study have examined the ability of baroreceptors in chronically hypertensive rabbits to reset rapidly during acute changes in carotid sinus pressure (31). Rapid resetting in response to an increase in carotid sinus holding pressure was impaired in the hypertensive rabbits whereas resetting in response to lowering the holding pressure was preserved. Decreased formation of PGI_2 in the hypertensive rabbits cannot explain the impairment of upwards resetting. Based on the present study, decreased PGI_2 should have augmented rapid resetting at the higher holding pressure.

Acknowledgments

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