Kor J Physiol (1995) 29(2), 279-289

Effect of Blood Pressure on Contractility of Vascular Smooth Muscle and Endothelium-Dependent Relaxation

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=ABSTRACT=

This study was designed 1) to develop a hypertensive animal model in which the blood pressures (BPs) of symmetric regions (right and left upper extremities) are significantly different and 2) to test the effect of BP per se on the contractility and endothelium-dependent relaxation of vascular smooth muscle. Rabbits were anesthetized with sodium pentobarbital and ventilated with room air via animal respirator. The transverse aorta was exposed through the left second intercostal space and the lumen of the aorta was narrowed partially by ligation using 3 - 0 silk and a probe at a point between the origins of the brachiocephalic trunk and the left subclavian artery. Four to eight weeks postoperatively, BPs were measured in the carotid artery as the high BP area (proximal to coactation site) and in the femoral artery as the low BP area (distal to coarctation site). In the animal model, pressure-overload hypertension was developed and the BP of the right subclavian artery was higher than that of the left subclavian artery. The concentrations of circulating epinephrine, norepinephrine, angiotensin I, and angiotensin II were measured. The right and left subclavian arteries and their branches were used for isometric tension recording in organ baths and their responsiveness to phenylephrine, serotonin, acetylcholine, and sodium nitroprusside were examined. The BPs of carotid and femoral artery in control animals were 116±12/75±9 mmHg (mean±SEM) and 130±16/68±9 mmHg respectively, while those of carotid and femoral artery in the hypertensive animals were 172±6/111±10 mmHg and 136±4/100±9 mmHg respectively. There were no significant differences in the concentrations of circulating epinephrine, norepinephrine, angiotensin I, and angiotensin II between controls and the animal models. No significant differences were found in the vascular sensitivities to phenylephrine and serotonin between the high pressure-exposed vessels and the low pressure-exposed vessels. However, the endothelium-dependent relaxation to acetylcholine and nitroprusside-induced relaxation showed significant differences between the high pressure-exposed and the low pressure-exposed subclavian arteries.

From the above results, we suggest that the contractility of vascular smooth muscle is unchanged by the elevated pressure per se. However, the endothelium-dependent relaxation to acetylcholine and the nitroprusside-induced relaxation are attenuated by pressure.

Key Words: A modified coactation hypertensive animal model, Endothelium-dependent relaxation, Nitroprusside, Symmetric arteries

INTRODUCTION

Hypertension is recognized as a disease of the vascular system and is characterized by elevated BP. Thickening of Arterial walls and enhanced vasoconstrictor sensitivity of the vascular smooth muscle are thought to be major contributors to the elevated vascular resistance responsible for the maintenance of hypertension (Webb RC, 1984) The elevated pressure per se in hypertension is believed to be a major factor in structural vascular changes associated with the disease (Folkow B, 1978). However, its exact role in changes in vascular smooth muscle sensitivity in hypertension has not been fully delineated. Early studies by Hansen et al (1974) and Berecek and Bohr (1977) demonstrated that elevated arterial pressure is not necessary for the expression of enhanced vasoconstrictor sensitivity in hypertension. However, these studies do not exclude a possibility that neurohumoral changes may modify functional properties of vascular smooth muscle in hypertension. On the contrary, Bell and Bohr (1991) reported that pressure per se plays a role in altered vascular smooth muscle responses to serotonin associated with hypertension. However, this study does not exclude a possibility that there may be a difference in sensitivity to vasoactive substances between thoracic and abdominal aorta. In an animal, the right and left sides of the body are symmetrical and the function of each side is similar. Therefore, one might expect that there would be no difference in the sensitivities to vasoactive substances between right and left sided blood vessels. In fact, there are no differences in the sensitivities to phenylephrine and serotonin between right and left subclavian arteries and their branches (unpublished data).

Therefore, we tried to develop a coarctation hypertensive animal model in which the BPs of right and left upper extremities are significantly different. In the animal model, we have tested the effect of BP per se on the contractility of vascular smooth muscle and endothelium-dependent relaxation.

MATERIAL AND METHODS

Animal preparation

Rabbits of either sex, weighing about 2.5 kg, were anesthetized with intravenous pentobarbital sodium (40 mg/kg), intubated, and ventilated with room air via an animal ventilator (Ugo Basile). The ventilation rate was 35-40 breaths/min, tidal volume was 15 ml. The respiratory rate was adjusted to keep the blood pH in the physiological range. The transverse aorta was exposed through the second intercostal space and ligated partially using 3 - 0 silk and probe (OD 3 mm) (n=9) (Fig. 1, A). Since the proximal part of the coarctation site is at a high pressure and the distal part of the site is at a low pressure, we could anticipate that the right subclavian artery and its branches would be exposed to high pressure and left subclavian artery and its branches to low pressure. In 9 additional control rabbits, the ring of silk too large to constrict the aorta was similarly placed (OD 10 mm or more). This group served as sham-operated normotensive control. Postoperatively, broad spectrum antibiotics were applied to the rabbits for 2 days.

Four to eight weeks postoperatively, rabbits were anesthetized with intravenous pentobarbital sodium, intubated, and ventilated with room air via an animal ventilator. The carotid artery and femoral artery were cannulated for BP measurements. The cannulas from carotid and femoral arteries were connected to a BP transducer via a 3-way valve (Fig. 1, B). With this set-up, we could use one BP transducer and one amplifier to measure the pressures of two arteries and lessen the error occurring from the use of different pressure transducers and different amplifiers to measure these BPs. The arterial blood was sampled from the carotid artery cannula to measure the levels of circulating epineph-

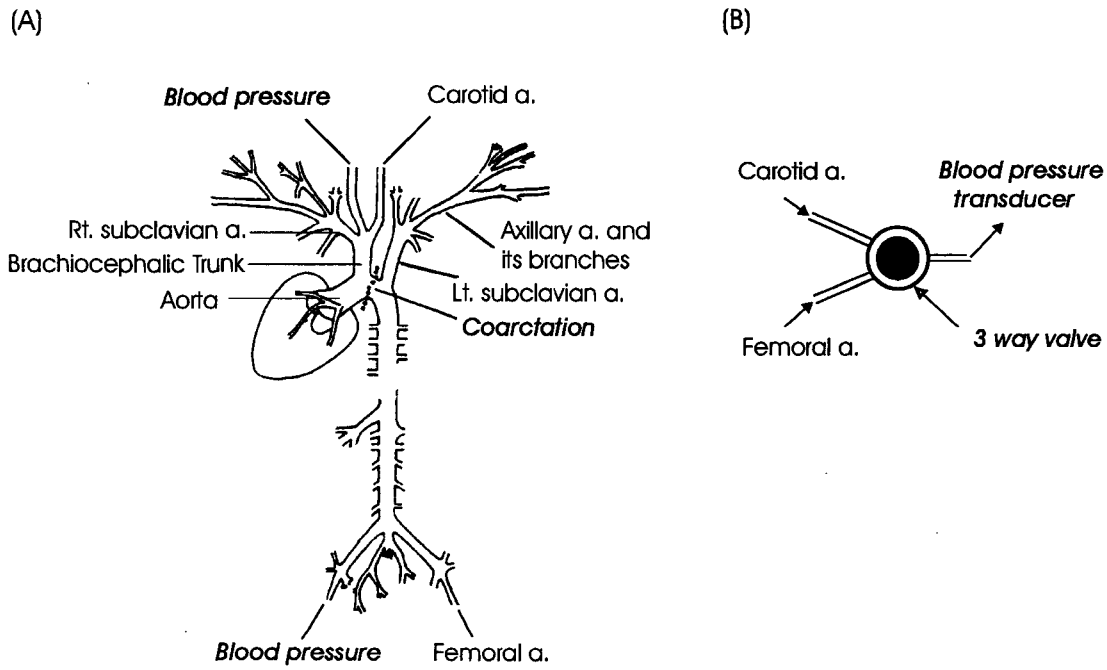

Fig. 1. A schematic representation of the major branches of the arterial tree, the sites of coarctation and measuring blood pressure (A), and blood pressure measuring system (B).

rine, norepinephrine, aniotensin I, and angiotensin II.

Mechanical responses

The right and left subclavian arteries and their branches were quickly removed and immersed in cold modified Krebs Ringer bicarbonate solution. The subclavian arteries were cleaned of connective tissue and 2 rings of the right and left subclavian arteries were taken at 5 mm proximal from the site of bifurcation to the axillary artery. In addition, branches of right and left subclavian arteries perforating into muscle (small artery) were taken for isometric tension recording.

Mechanical responses were recorded from the ring segments (subclavian artery, 1.0~1.5 mm and its branches, 1 mm). Each ring was suspended by two L-shaped stainless steel pins(2 mm for subclavian artery and 70 μm for its branch): one pin was anchored in an organ chamber (0.5 ml) and the other connected to a mechano-transducer (Grass, FT-03), which was connected to a three dimensional manipulator. The rings were mounted under optimal resting tensions (1.5 g for subclavian artery and 600 mg for its branch) and the muscle chamber was perfused with modified Krebs Ringer bicarbonate solution maintained at 36.5℃, at a constant flow rate of 4 ml/min using a peristaltic pump (Vision). The optimal resting tensions were determined by comparing the tension developed in high K^+ solution under different resting tensions. The tissues were equilibrated for 60 min at the optimal resting tension for maximal tension development in response to high-K^+ solution. A cumulative relaxation curve to acetylcholine was obtained in each ring with intact endothelium. The endothelial cells were removed mechanically using the method of Furchgott and Zawadzki (1980), i.e., the internal surface of the vessel was rubbed gently by a moistened cotton ball and successful removal of functional endothelial

cells was assumed from the absence of any detectable relaxation by acetylcholine (from 10^{-8} M to 10^{-6} M) in preparations precontracted with phenylephrine. A cumulative contraction curve to phenylephrine and serotonin and relaxation curve to sodium nitroprusside were obtained in denuded rings.

Measurement of the concentrations of epinephrine, norepinephrine, angiotensin I, and angiotensin II

Epinephrine and norepinephrine: Blood samples from the carotid artery were transferred into chilled (0℃) tubes containing heparin (500 IU/ml) and EDTA (10 mg/ml heparin) and were centrifuged. Plasma was obtained and stored at -70℃ until assayed for its catecholamine content by liquid chromatography in combination with electrochemical detection using the method of Scheurink et al (1989).

Angiotensin I and angiotensin II: Blood was collected with EDTA for the measurement of plama renin activity. For the measurement of the plasma concentration of angiotensin II, blood was collected into cooled syringes containing an enzyme inhibitor solution (Bunkenburg et al, 1991) to prevent in vitro generation and/or degradation of angiotensin II. Plasma was stored at -70℃ until the time of the assay.

Determination of plasma renin activity was made by the angiotensin I antibody trapping method (Poulsen & Jorgensen, 1974). Plasma angiotensinogen was determined by incubation of plasma with an excess of human renin as previously described by Menard & Catt (1972). The angiotensin I generated during the incubation step was quantitated by radioimmunoassay.

Plasma angiotensin II concentrations were measured by radioimmunoassay after extraction of angiotensin II from the plasma with phenylsilyl silica and separation from other immunoreactive material by high-performance liquid chromatography as previously decrived by Nussberger et al (1985).

Solutions and drugs

The ionic composition of the Krebs Ringer bicarbonate solution was as follows (in mM): NaCl 118.3, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.22, $CaCl_2$ 2.5, $NaHCO_3$ 25.0, CaEDTA 0.016, and glucose 11.1. The solution was aerated with 95% O_2-5% CO_2(pH 7.3-7.4). High-K^+ solution (29.6 mM KCl) was prepared by replacing NaCl with KCl.

Drugs used were acetylcholine chloride, L-phenylephrine, serotonin, and sodium nitroprusside (all from Sigma, U.S.A.).

Statistics

Experimental values were expressed as means ± SEM for n separate experiments. Statistical significance was determined using paired Students' t-test, and probabilities of less than 5% ($p<0.05$) were considered significant.

RESULTS

All animals used in this study remained in good health during the postoperative period with no signs of impaired growth. At necropsy, all organs appeared normal with the exception of myocardial hypertrophy.

The change of BP in the experimental animal model

The systolic and diastolic pressures in the carotid artery were significantly increased in the experimental animals, compared with the controls ($p<0.01$) (Fig. 2 and Table 1). In the femoral artery, there was no significant difference in the systolic pressures between the control and experimental rabbits. However, the diastolic BP was significantly increased in the experimental animals, compared with the controls ($p<0.01$).

Normally, there is a difference in the BP between the carotid artery and the femoral artery and no difference between the right extremity and the left

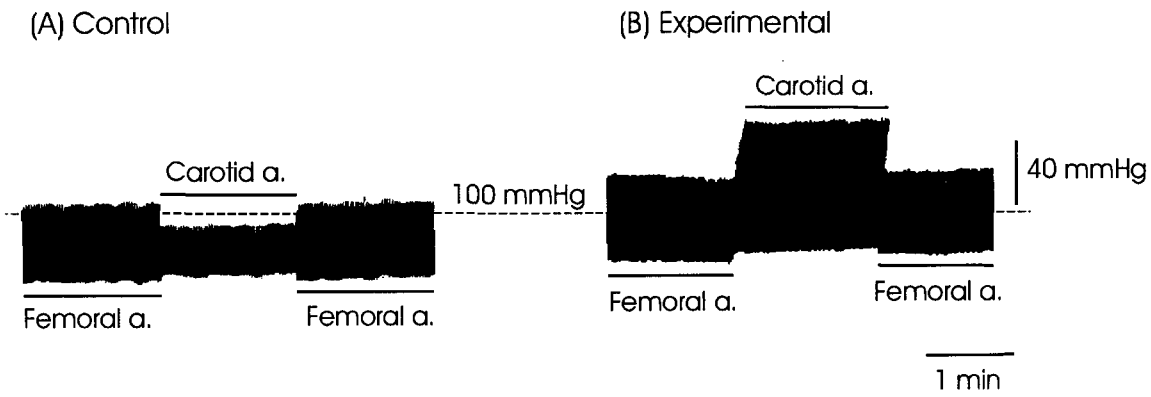

Fig. 2. Representative recordings of blood pressures measured at carotid and femoral arteries, in control (A) and experimental rabbit (B).

Table 1. Blood pressure of the carotid and femoral arteries of the control and the experimental animal model (n=9)

		Blood pressure	
		Control	Coarctation model
Systolic BP	Carotid a.	116±13(mmHg)	172±6**
	Femoral a.	130±16	136±4
Diastolic BP	Carotid a.	75±9	110±10†
	Femoral a.	68±9	100±†

Values are mean ± SEM. ** $p<0.01$ between carotid and femoral blood pressures of the experimental animal. $p<0.01$ between the control and the experimental animal.

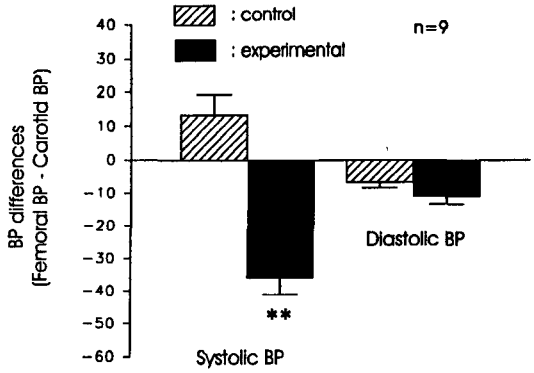

Fig. 3. The differences in blood pressure between femoral and carotid arteries in the control and the experimental animals. Results are shown as means ± SEM.

extremity. In control rabbits, the systolic BP of the femoral artery was 14 mmHg greater than that of the carotid artery and diastolic BP of the femoral artery was 7 mmHg lower than that of the carotid artery (Fig. 3). In experimental rabbits, the systolic BP of the femoral artery was 36 mmHg lower than that of the carotid artery and diastolic BP of the femoral artery was 11 mmHg lower than that of the carotid artery. Considering the pressure differences within the control group, the pressure differences of the model between the high pressure area (right subclavian artery and its branches) and the low pressure area (left subclavian artery and its branches) were about 50 mmHg in systolic pressure and 4 mmHg in diastolic pressure (Fig. 3). Thus, there was a significant difference in the systolic pressure ($p<0.01$) but not in the diastolic pressure ($p>0.05$).

From these results, we could conclude that the high pressure region of the animal model is hypertensive in systolic and diastolic pressure whereas the

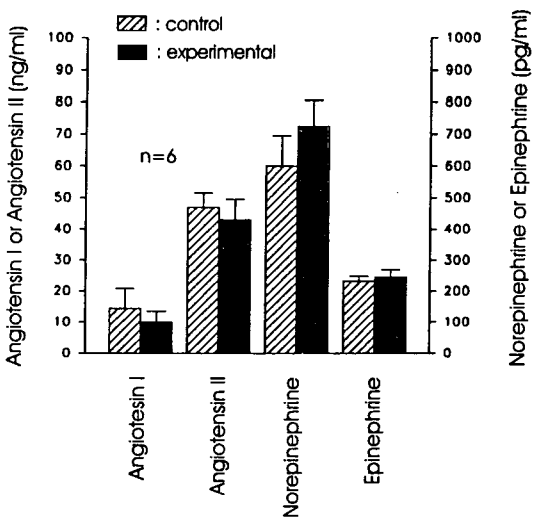

Fig. 4. Plasma concentrations of angiotensin I, angiotensin II, norepinephrine, and epinephrine in the control and the experimental animals. Results are shown as means ±SEM.

low pressure region is hypertensive only in diastolic pressure.

The plasma concentrations of epinephrine, norepinephrine, angiotensin I, and angiotensin II

There were no significant differences in the plasma concentrations of epinephrine, norepinephrine, angiotensin I, and angiotensin II between controls and experimental animals ($p>0.05$) (Fig. 4).

Mechanical responses

Vascular contractile sensitivities to serotonin and phenylephrine in the three groups (subclavian arteries of the controls, left and right subclavian arteries of the animal model) are shown in Fig 5. There were no significant differences in the sensitivities to serotonin and phenylephrine between these subclavian arteries.($p>0.05$).

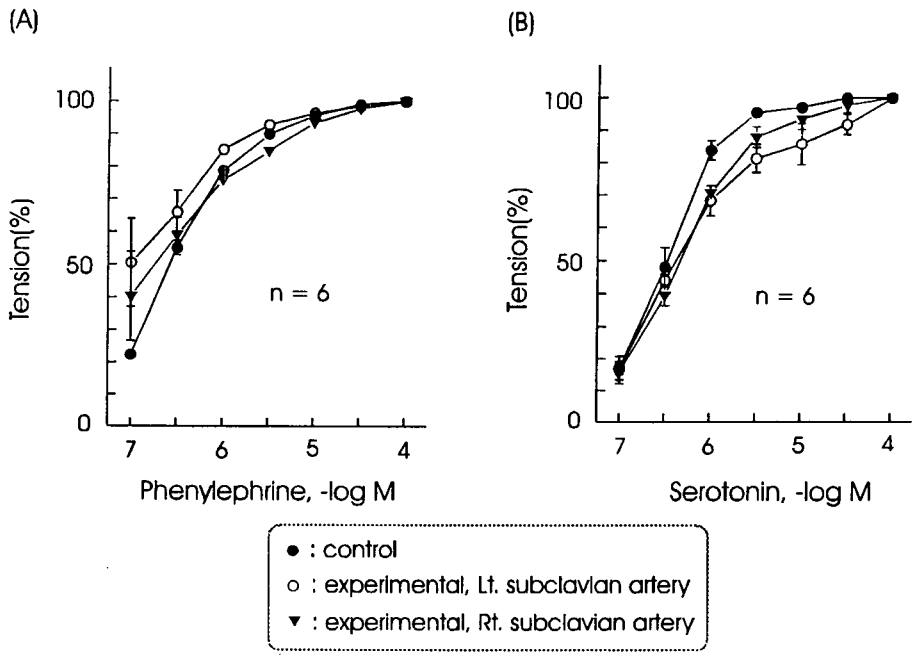

Fig. 5. Concentration-response curves to phenylephrine (A) and serotonin (B) in right (exposed to a high blood pressure) and left (exposed to a low blood pressure) subclavian arterial rings of experimental animals and subclavian arterial rings of control animals. Results are shown as means ±SEM and expressed as a percentage of the contraction induced by 10^{-4} M phenylephrine or serotonin.

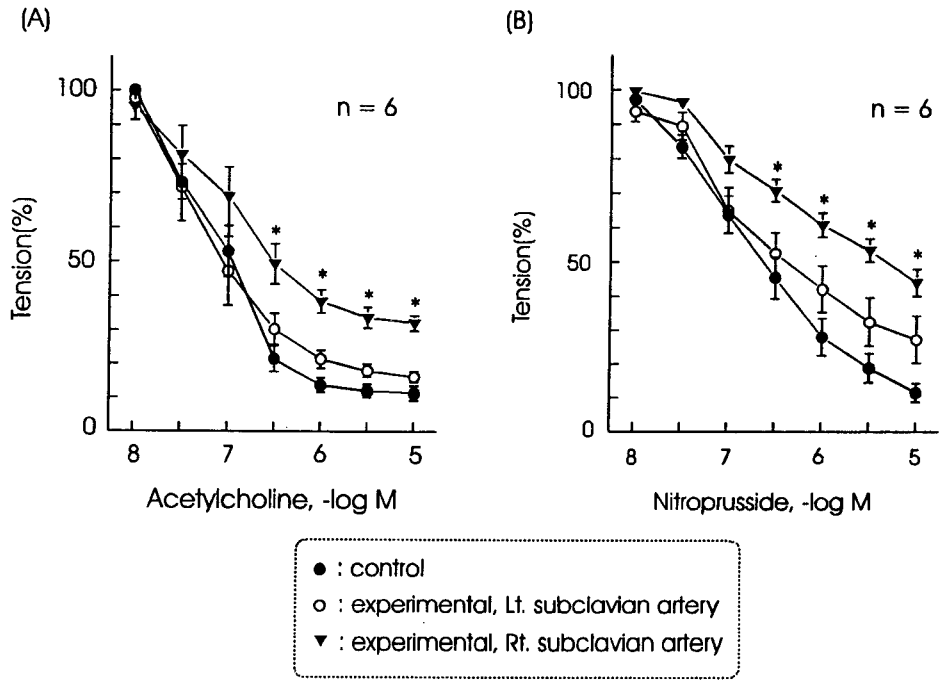

*Fig. 6. Endothelium-dependent relaxation to acetylcholine (A) or nitroprusside-induced endothelium-independent relaxation (B) recorded in right (exposed to high blood pressure) and left (exposed to low blood pressure) subclavian arterial rings of the experimental animals and subclavian arterial rings of the control animals. Results are shown as mean ±SEM and are expressed as a percentage of the contraction induced by 3×10^{-6} M phenylephrine. * means significant difference between right and left subclavian arterial rings ($p<0.05$).*

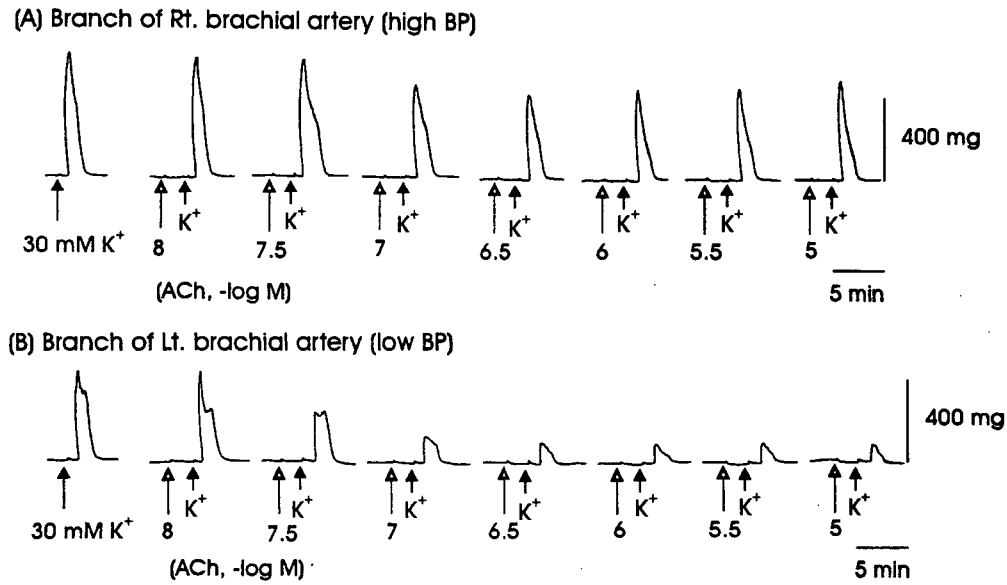

Fig. 7. A representative recording showing the effect of acetylcholine on endothelium in arterial rings prepared from the perforating branches of right and left subclavian arteries of an experimental rabbit.

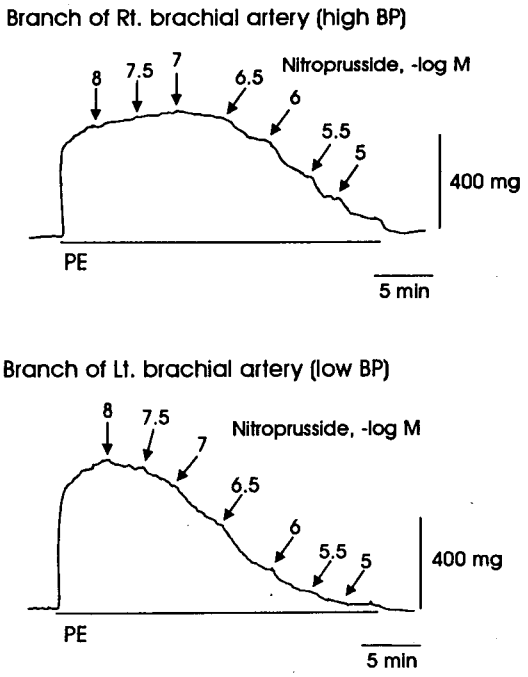

Fig. 8. A representative recording showing nitroprusside-induced relaxation in the arterial rings prepared from the perforating branches of right and left subclavian arteries of an experimental rabbit.

Endothelium-dependent relaxation to acetylcholine in the subclavian arterial ring precontracted with phenylephrine is shown in Fig. 6, A. The endothelium-dependent relaxations were significantly impaired in the right subclavian arteries of experimental animals, compared with control and with the left subclavian arteries of experimental animals. Endothelium-independent relaxation to sodium nitroprusside in the arterial ring without endothelium precontracted with phenylephrine is shown in Fig. 6, B. The endothelium-independent relaxations to nitroprusside were significantly impaired in the right subclavian arteries of experimental animals, compared with control and with the left subclavian arteries of experimental animals.

Small arteries showed similar responses (Fig. 7 and Fig. 8). With an increase of the concentration of acetylcholine, the contraction induced by 29.6 mM KCl was decreased. The magnitude of the decrease was greater in the small arteries exposed to low pressure than that of the small arteries exposed to high pressure. Nitroprusside-induced relaxation in the arterial rings precontracted with phenylephrine (10^{-5} M) was attenuated in the small arteries exposed to high pressure, compared with the small arteries exposed to low pressure.

DISCUSSION

In the present study, we have attempted to examine the potential role of pressure in changes in hypertension by exploiting the unique hemodynamic characteristics of coarctation hypertension. This model allows us to use arteries that have been exposed to the same humoral and neural influences of hypertension but to different pressures. Another advantage of this model is that symmetric arteries, the right and left subclavian arteries and their branches, can be studied. This could exclude the possibility of a difference of sensitivity to vasoactive substances according to the regions from which the vessels were taken. In addition, this model allows us to use resistant arteries (small arteries, perforating branches of right and left subclavian arteries) that have been exposed to different pressures. As the resistance of the circulation is mainly determined by resistant arteries, the effect of pressure per se on resistant arteries should be investigated to clarify the mechanism of hypertension. This is the only model which can be used to investigate the effect of pressure per se on resistant arteries. Therefore, the model possesses advantages over other means of examining pressure effects in hypertension. Though the model has these advantages, the disadvantage of the model is that the low pressure region is not normotensive but hypertensive in diastolic pressure. The reasons that there are no significant differences in the blood concentrations of epinephrine, norepinephrine, angiotensin I and angiotensin II between control and the experimental animals are not readily

apparent. However, two possibilities could be suggested. One of the possible reasons is that lowered pressure by coaractation in the region distal to ligation is not sufficient to acivate the renin-angiotensin system. The other reason is that the concentrations of these humorals had been increased initially and had then normalized 4～8 weeks postoperatively.

The current study shows that endothelium-dependent relaxation to acetylcholine and endothelium-independent relaxation to sodium nitroprusside are significantly attenuated in the vessel from the high pressure region of the experimental animals. Impairment of endothelium-dependent relaxation has been demonstrated in many models of hypertension, using a variety of techniques (Chen & Sanders, 1991; King et al, 1991; Lüscher et al, 1988; Lüscher et al, 1987; Martasek et al, 1991; Nakamura & Prewitt, 1991; Radomski et al, 1990). Acetylcholine or other EDRF agonists produce impaired relaxation responses in spontaneously hypertensive rats (Lüscher et al, 1988), Dahl salt-sensitive rats (Lüscher et al, 1987), and one-kidney, one clip hypertensive rats (Nakamura & Prewitt, 1991). Our observation that acetylcholine is less effective in inducing relaxation in subclavian arterial rings of a high pressure region in the experimental animals is consistent with the observations in these other hypertensive conditions. However, it is difficult to speculate how elevated pressure might impair endothelium-dependent relaxation to acetylcholine, since that mechanism is not fully understood.

Vascular hyperresponsiveness to arachidonic acid released by acetylcholine (Lockette & Webb, 1985; Singer & Peach, 1983) could counteract endothelium-dependent relaxation by acetylcholine. However, Lockette et al (1986) have reported that impaired arterial responses to acetylcholine in hypertensive rats do not result from stimulation of the release of arachidonic acid. In our study, endothelium-independent relaxation to sodium nitroprusside is also attenuated in subclavian arterial rings of the high pressure region in the experimental animals. As nitrovasodilators dilate blood vessels by releasing nitric oxide (NO), the present study may suggest that the sensitivity of vascular smooth muscle to NO is decreased by elevated pressure per se.

It is well established that elevated arterial pressure is a major contributor to arterial medial hypertrophy in hypertension (Folkow B, 1978). Medial thickening in an artery may limit the access of released EDRF to underlying smooth cells, rendering them less responsive to the effects of EDRF. Neural and/or humoral factors have also been reported to contribute to medial thickening of arteries in hypertension (Bevan, 1975; Overbeck, 1979). Consequently, different degrees of medial thickening caused by pressure per se in the high pressure region vs. the low pressure region may play a role in the different sensitivity to acetylcholine observed between those vessels.

It is possible that pressure per se may affect endothelium-dependent relaxation by affecting endothelial function directly. It has been reported that an enhanced endothelial turnover rate in hypertensive thoracic aorta of rat with aortic ligation but not in the abdominal aorta of these rats which were not exposed to high pressure (Owens & Reidy, 1985). Endothelial turnover rate has been suggested to indicate endothelial damage or disruption better than visual examination of the endothelial surface (Owens & Reidy, 1985). It could be suggested that the function of damaged and newly developed endothelium is depressed and the production of EDRF is decreased, compared with normal endothelium.

In contrast to the effects on endothelium- dependent relaxation to acetylcholine and endothelium-independent relaxation to nitroprusside, vascular sensitivities to serotonin and phenylephrine were not changed in the hypertensive animal models, compared with the control animals. This finding differs from the observation that vascular sensitivity to serotonin was increased in hypertension (Mecca

& Webb, 1984). They have reported that increased vascular sensitivity to serotonin in hypertension is mediated by a larger release of Ca^{2+} from intracellular stores. Since hypertension was evoked by application of steroids in the animals used in the experiments, the increased sensitivity to serotonin could be suggested to be the effect of the steroid administered.

In summary, we have developed a hypertensive animal model in which the BPs of symmetric regions are significantly different. With the use of this hypertensive animal model, we have demonstrated that endothelium-dependent relaxation to acetylcholine and endothelium-independent relaxation to nitroprusside is attenuated in the vessels exposed to high pressure. In contrast to the effects of the vasodilators, the vascular sensitivity to serotonin or phenylephrine was not significantly changed in the vessels exposed to high pressure. The discrepancy between the effect of the vasodilator and that of vasocontrictors remains to be determined.

ACKNOWLEDGEMENTS

This study was supported by a 1994 RESEARCH GRANT FOR BASIC MEDICINE from the MINISTRY OF EDUCATION.

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