BIOMECHANICAL RESPONSE OF ARTERIAL WALL TO DOCA-SALT HYPERTENSION IN THE MATURED RAT

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INTRODUCTION

Effects of hypertension on the morphology and mechanical properties of arterial wall have been extensively studied using animal models, including Goldblatt hypertension and DOCA (Deoxycorti costerone acetate)-salt hypertension [1-3]. In Goldblatt hypertension, the serum concentration of angiotension is increased by the constriction of one of the renal arteries, which contracts large and peripheral arteries, and induces systemic hypertension. In DOCA-salt hypertension, blood pressure is elevated by the increase of circulating blood volume, which is similar to human hypertension. Many previous studies have been done by applying these methods to relatively young, growing animals [2,3].

In the present study, DOCA-salt hypertension was induced in maturated rats, as a model of human hypertension, and the biomechanical properties and wall dimensions of their common carotid arteries were investigated.

METHODS

Arterial Specimen

The treatment for DOCA-salt hypertension was applied to 23 male Wistar rats aged 16 weeks, weighing 534 ± 31 g (mean ± standard deviation), by the unilateral nephrectomy, subcutaneous implantation of silicone rubber impregnated with DOCA (100 mg/kg body weight), and daily drinking of 1% NaCl solution. Systolic blood pressure, which was measured with tail-plethysmography once a week, gradually increased with time, and hypertension (over 160 mmHg) was developed in approximately 55 % of the animals (13 rats) at 10 or 16 weeks. Immediately before each rat was euthanized at 10 or 16 weeks postoperatively, blood pressure was measured with a catheter-tip, implantable pressure transducer. Then, the left common carotid artery (approximately 30 mm in length) was excised and divided into a proximal (15 mm long) and a distal (5 mm long) portions for biomechanical tests and dimensional measurements, respectively. Non-treated 7 rats aged 32 weeks, weighing 739 ± 49 g, were used to obtain control data.

Mechanical Testing

The proximal portion of each arterial segment was stretched to its in vivo axial length in a tissue bath filled with aerated Krebs-Ringer solution of 37˚C. It was then quasi-statically inflated and deflated between 0 and 250 mmHg to obtain internal pressure (Pi)-external diameter (Do) data under normal (Krebs-Ringer solution), active (administration of norepinephrine), and passive (administration of papaverine) conditions. Do was obtained with a CCD camera and a video dimension analyzer, while Pi was measured with a fluid-filled pressure transducer.

Four rings having the thickness of 0.5 mm were cut out from the distal portion of each arterial segment for the measurement of internal and external diameter at no load state.

Data Analysis

Assuming the incompressibility of wall, wall dimensions at Pi were calculated. Wall circumferential stress (σ_θ) was calculated from systolic blood pressure (Ps), wall thickness (T), and internal radius (Ri) both at Ps, using Laplacian law; $\sigma_\theta = PsT/Ri$.

Arterial contractility was evaluated with the diameter response ($\delta Do/Do$), which is defined as the relative reduction of Do at each pressure from passive to normal conditions, or from passive to active conditions. This parameter represents the degree of smooth muscle tone or smooth muscle cell activation. Wall stiffness was expressed by the stiffness parameter (β') [4], which is the normalized slope of a Pi-Do curve at each pressure.

RESULTS

In the control rats, the averaged Pi-Do curve obtained under the normal condition was almost the same as that under the passive condition (Fig. 1). In the hypertensive rats, however, the curves under the normal condition shifted toward the left from those under the passive condition. The diameter reduction developed by norepinephrine (active condition) was much larger in the hypertensive rats than in the control ones except for that in a very high pressure range. The pressures at flexion points in the Pi-Do curves obtained

under the active condition [5] were much higher in the DOCA-salt rats than in the control ones.

There were significant positive correlations between Ps and δDo/Do at Ps, and between Ps and β' at Ps under the normal condition both at 10 and 16 weeks (Table 1). At 10 weeks postoperatively, σ_θ at Ps significantly correlated with Ps. However, this was not the case at 16 weeks, because wall thickness/internal radius ratio became larger in the hypertensive rats than in the control rats.

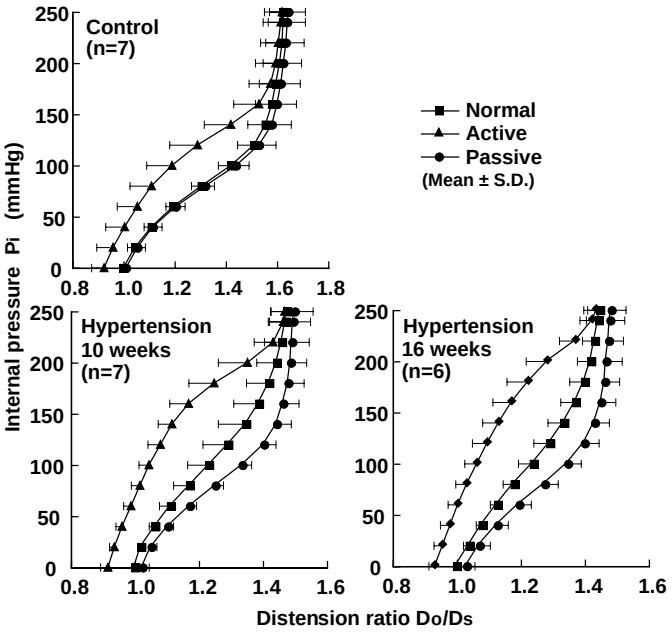

Fig. 1 Internal pressure-distension ratio relationships of the common carotid artery from control and hypertensive (Ps ≥160 mmHg) rats. Ds = Do at 0 mmHg under the normal condition.

Table 1 Correlation coefficients between the systolic pressure (Ps) measured immediately before animals were killed and the mechanical parameters of wall under the normal condition. Statistically significant correlations were observed in all the parameters except for σ_θ at 16 weeks (indicated by a parenthesis, p > 0.5%)

Period	10 weeks	16 weeks
δDo/Do	0.558	0.628
β'	0.526	0.495
σ_θ	0.640	(0.402)

δDo/Do, diameter response; β', stiffness parameter; σ_θ, wall circumferential stress, all at Ps.

DISCUSSION

There was a significant correlation between σ_θ and Ps at 10 weeks (Table 1). However, the correlation disappeared at 16 weeks, which suggests that wall circumferential stress is restored to a control level after a prolonged period of hypertension. Sumitani et al. [1] induced Goldblatt hypertension in rats aged 12 weeks, and observed that σ_θ in the thoracic aorta was almost similar to that in normotensive rats at 12 weeks after the induction of hypertension. These two results indicate that arterial wall responds to Goldblatt hypertension earlier than to DOCA-salt hypertension because of the direct effect of angiotension on the wall in the Goldblatt model.

Using Sprague Dawley rats aged 4 weeks, Berthon et al. [2] have recently shown that σ_θ in the carotid artery was significantly decreased by 8-week DOCA-salt hypertension compared to normotensive animals. Wall stress may have been restored to a control level by 8 weeks, and become lower than a normal level at 8 weeks because of excessive wall hypertrophy. Wall distensibility was almost the same between the hypertensive and normotensive rats. Matsumoto and Hayashi [3] induced Goldblatt hypertension in Wistar rats aged 8 to 9 weeks, and observed that σ_θ in the thoracic aorta of hypertensive rats was similar to a normotensive level already at 2 weeks postoperatively, whereas wall stiffness was significantly larger in hypertensive rats than in normotensive ones even at 16 weeks. These and the present results suggest that, in response to hypertension, wall stress and stiffness are restored to normal levels more slowly in mature animals than in growing animals.

There were significant correlations between δDo/Do under the normal condition and Ps both at 10 and 16 weeks (Table 1). Fridez et al. [6] induced hypertension in 8-week old Wistar rats by the total ligation of the aorta between the two kidneys, and observed that smooth muscle tone in the common carotid artery rapidly increased within a few days, then gradually decreased, and returned to a normotensive level at 8 weeks. These results indicate that the sensitivity of vascular smooth muscle cell to hypertension is less in mature animals than in growing ones.

In conclusion, the response of arterial wall to the elevation of blood pressure seems to appear more slowly in DOCA-salt hypertension than in Goldblatt hypertension, and in mature animals than in growing ones.

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