Mechanical Properties of Carotid Arteries
From DOCA Hypertensive Swine
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Richard A. Murphy, and David F. Bohr

Carotid arteries from control and deoxycorticosterone acetate (DOCA) hypertensive swine were examined for alterations in structure and in contractile properties. Vessels were excised 7 weeks after subcutaneous implantation of the steroid and subsequent elevation in mean arterial pressure from 102 to 133 mm Hg. The carotid media was 1.8 times thicker in arteries from hypertensive animals than in arteries from control animals. This enlargement was associated with an increase in muscle mass, as the fraction of the media composed of smooth muscle cells remained unchanged. Maximal active stress induced by several agonists normalized for cell cross-sectional area was unaltered. No change was observed in sensitivity or maximal response to norepinephrine, histamine, or KCl depolarization. Isotonic shortening rates were also comparable, as was the time course of shortening velocity to a constant afterload during tonic contractions. It is concluded that an enlargement of the carotid media develops in this model of hypertension. However, this response is not associated with detectable alterations in contractile system function. (Hypertension 1989; 13:102–109)

The development of deoxycorticosterone acetate (DOCA)-induced hypertension in the pig has been described in detailed studies on whole animal1–3 and isolated vascular4–5 preparations. The elevation of arterial blood pressure reflects an increase in peripheral vascular resistance that may have several causes. Two factors have considerable experimental support from studies of DOCA hypertension in the pig and rat. Structural changes (wall thickening or rarification of resistance vessels) with a decreased maximum vasodilator capacity (reviewed in Reference 6) are one factor. The second factor is increased vascular reactivity, which would contribute to elevated vascular tone.1,4,7–10

Changes involving the contractile apparatus in the vascular smooth muscle cells may also underlie chronic alterations in peripheral resistance. These could include altered Ca2+-dependencies, changes in myofilament lattice or cytoskeletal geometry, or possibly myofilament protein changes influencing chemomechanical transduction (reviewed in Reference 11). Maximum active stress was found to be lower in some in vitro studies of arteries from DOCA hypertensive rats.10,12 However, the assessment of contractile system function in smooth muscle is difficult and changes in stress-generating capacity do not necessarily involve the contractile apparatus per se. The many issues involved have been previously reviewed.13,14 The primary objective of this study was to determine whether altered contractile system function is a factor that must be considered in the etiology of DOCA-induced hypertension in swine.

Materials and Methods
Preparation of Hypertensive Animals
Male Chester White pigs 2–3 months old were treated as described previously.2,3 The animals were housed in metabolic cages and were fed Purina Pig Growena and tap water ad libitum. The average daily sodium intake was 150–175 meq/day. No supplemental sodium was given. Chronic indwelling catheters in most animals were used to monitor
hemodynamic variables. Animals received subcutaneous implantations of either DOCA (Sigma Chemical Co., St. Louis, Missouri; 100 mg/kg) in a silastic rubber carrier (Dow Corning, Midland, Michigan; DOCA:silastic = 1:2) or a pure silastic rubber strip. Steroid-free implants produced no changes in any measured parameter in control animals. Animals receiving DOCA treatment showed increased mean arterial pressures within 48 hours of implantation. Pressures continued to rise to 30–40 mm Hg above preimplant values in 10–14 days and remained elevated until termination. Animals were terminated with an overdose of sodium pentobarbital.

Tissue Preparation

Carotid arteries from control and hypertensive animals were excised and rinsed with cold physiological salt solution (PSS). For use in these studies, one artery from each animal was sealed in a vial containing about 200 ml PSS. Vials were packed on ice at the University of Michigan and sent by air express for delivery on the following morning to the University of Virginia or the University of Texas Southwestern Medical Center at Dallas. Medial segments were dissected and experiments performed immediately after arrival. Full medial thickness strips were prepared by the method of Driska et al. and used in all isometric experiments in which maximum steady-state stresses were sought. All control data, with the exception of that for isotonic experiments, were obtained with arteries from Michigan. Thin strips with reduced diffusion paths were dissected for isotonic experiments in which mechanical time courses were measured. Tissue preparations were 1–2 mm wide and 8–10 mm long. Full medial thicknesses were 0.22–0.41 mm; thin strips were approximately half these values.

The PSS was composed of (mM): NaCl 140.0, KCl 4.7, CaCl₂ 1.6, MgSO₄ 1.2, Na₂HPO₄ 1.2, Na₂EDTA 0.02, D-glucose 5.6, and morpholinopropanesulfonic acid (MOPS) buffer 2.0. Solution pH was adjusted to 7.4 at the experimental temperature of 37°C and gassed with 100% O₂. High-potassium solution (K⁺-PSS) was made by equimolar substitution of KCl for NaCl to bring the final potassium concentration to 109.7 mM. Intermediate K⁺ concentrations were obtained by mixing PSS and K⁺-PSS. The concentration of NaCl was adjusted to maintain osmolarity when CaCl₂ concentration was varied. Concentrated stock solutions of histamine and norepinephrine (Sigma Chemical Co.) were made daily, kept on ice in the dark, and diluted on use.

Isometric and Isotonic Measurements

Three to five strips were prepared from an artery. Each was hung in a 25-ml jacketed chamber from a Grass FT.03C force transducer (Quincy, Massachusetts) using a mylar tape and a McKenzie clip and clamped in a lower support whose position could be adjusted with a calibrated mechanical drive. Force was recorded with a Grass Model 7 Polygraph. Tissues were equilibrated 1 hour in PSS at 37°C before stress-length curves were obtained to determine the optimal tissue length (L₀) for maximal active stress (S₀) development (see “Results”). Stresses were calculated from force measurements by using tissue cross-sectional areas estimated by dividing tissue wet weight by tissue density (1.05 g/cm³) and L₀. Isotonic measurements were made on thin strips mounted at L₀ in an electronic lever apparatus (V. Claes, Antwerp, Belgium). Quick releases to a fixed afterload of 0.1 S₀ were performed at different times after stimulation with K⁺-PSS. Force and length signals were displayed on a Brush 220 strip chart recorder (Gould, Inc., Cleveland, Ohio). Values of isotonic shortening velocity were determined with a linear regression program, which estimates ΔL/Δt at the moment of quick release from the natural logarithm of the normalized length versus time curve, using length values at times between 1.0 and 2.2 seconds after quick release. The lever system characteristics are described elsewhere.

Histology

After experimental protocols were completed, strips (one per animal) at L₀ were fixed at room temperature for 2 hours in 2.5% (vol/vol) glutaraldehyde, 0.1 M sodium cacodylate buffer (pH 7.2, 25°C), and 6.6% (wt/vol) sucrose. Strips were then removed from their holders and postfixed for 2 hours in a 1% osmium tetroxide, 0.1 M cacodylate buffer solution (pH 7.2). This was followed by staining in 3% uranyl acetate for 2 hours, dehydration in ethanol and acetone, and embedding in Polybed 812. Blocks were sectioned perpendicular to the long axis of the strip. Medial thickness was measured on thick sections (2 μm) with a microscope equipped with a filar ocular micrometer. Ultrathin sections (0.08 μm) were collected on formvar-coated copper grids, and eight to 15 nonoverlapping electron micrographs (magnification, ×3,600) of the cells in cross section were taken randomly over the media. Cell fractions were estimated from these micrographs by determining the point fraction of cells under a grid and by using points over the total area covered as the reference area. Cell fractions measured in sections from each of four quadrants of a strip were not significantly different, therefore sections from a single area were taken as representative. In addition, five to 10 serial photomicrographs (magnification, ×4,000) were taken to construct a montage across the media (intima to adventitia). The intimal boundary of the media was defined from the basal lamina. The border of the adventitia was defined from the last elastic lamina beyond which few smooth muscle cells, dense swirls of collagen fibrils, a number of fibroblasts, and patchy, if any, elastin were seen. Photomicrographs of the medial cross section were...
Morphology from the DOCA hypertensive animals (Table 2).

The availability of tissues from hypertensive swine in the Michigan program provided an opportunity to

results from serial micrographs showed that medial hypertrophy was also associated with increased lamellar width, while the numbers of lamellae were unchanged (Figure 1). Lamellae near the adventitia showed the greatest proportional increase in width. The number of lamellae and the cell fraction per lamella showed essentially no significant changes (Table 2, Figure 1).

Vessel Viability

The availability of tissues from hypertensive swine...
undertake this study, provided that vessels could be shipped to Virginia without variable alterations in their viability or responsiveness. This seemed feasible because locally collected carotid arteries maintained in zwitterionic-buffered (MOPS) PSS at 0–4°C remained viable for over 72 hours with no change in their stress-generation capacity in response to depolarization or in other estimates of activation including shortening velocity, crossbridge phosphorylation, or myoplasmic Ca²⁺ concentration. In practice, tissues prepared from vessels of six control and five hypertensive swine out of a total of 12 from each group shipped from Michigan gave no contraction on depolarization. Two such tissues were examined histologically and most cells were necrotic. The remaining tissues appeared to be normal: there were no significant differences in the stress-generating ability in the vessels of hypertensive or control swine from Michigan, or in either fresh or stored arteries collected in Virginia. No evidence of necrotic cells was observed in the histological work done with responsive tissues. These observations suggest that something (which we never identified) sometimes occurred in either tissue collection (solution composition errors, perhaps) or shipping (ice always remained on receipt) that led to tissue destruction. There was no suggestion that the factor, which led to variable reductions in tissue viability or responsiveness, was always present. We applied no selection criteria in the data analysis, including all tissues that responded on depolarization.

**Stress-Length Relations**

The passive and active stress-length relations were constructed for tissues from four DOCA and five control animals (Figure 2). Strips equilibrated in PSS were stretched to lengths at which tension was about 0.15 N, then rapidly shortened in known-length steps to obtain the passive force after quick release. Total force was that generated in K⁺-PSS. Responses were expressed as stress (force/tissue cross-sectional area) (Table 3), and lengths were normalized as fraction of Lₒ for maximal active force development. The ratio of passive-to-active force at Lₒ was 0.14±0.09 for tissues from control and 0.20±0.07 for tissues from hypertensive swine (p>0.4).

The entire passive stress-strain curve was described by the exponential relation: Sₑ=Sₒ e^[βA] where Sₑ is passive stress, Sₒ is maximal active stress, β is a constant reflecting the rate of increase of stiffness, and A is the normalized length, L/Lₒ. The stiffness constant β was calculated from the least-squares fit to a linearized form of the expression by using five to seven points from each tissue (r²>0.96). Values of β were 9.4±2.0 and 11.6±1.8 for medial tissues from control and hypertensive swine, respectively (p>0.4).

**Contractile Response to Agonists**

Concentration-response relations were determined on strips adjusted to Lₒ by using four stimulus conditions by varying external concentrations of KCl, norepinephrine, histamine, and CaCl₂ in the presence of 110 mM KCl (Figure 3). Strips were preincubated approximately 60 minutes in PSS containing zero CaCl₂, followed by an incubation for about 45 minutes in K⁺-PSS also containing zero calcium. Addition of depolarizing solution usually resulted in a transient contraction due to mobilization of remaining intracellular Ca²⁺ pools. The magnitude of these transient responses characteristically varied from 0.05 to 0.9 times the maximum measured force in K⁺-PSS. No apparent difference in this response was detected between the two groups. When the strips were fully relaxed, the bathing solution was changed to one containing calcium. The maximal response for any stimulus condition was measured after a new steady-state force had been achieved and maintained for 5 or more minutes. At low concentrations of potassium or of calcium, this could require 60–90 minutes. Under no conditions was there any difference in the
TABLE 3. Maximal Stress and EC₅₀ Values for Different Agonists

<table>
<thead>
<tr>
<th>Agonist (A)</th>
<th>[A]</th>
<th>Maximal stress (x10⁶ N/m²)</th>
<th>Control</th>
<th>DOCA</th>
<th>EC₅₀ Control</th>
<th>EC₅₀ DOCA</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCl 110 mM</td>
<td>2.6±0.19</td>
<td>2.6±0.27</td>
<td>1.35±0.04</td>
<td>22.6 mM</td>
<td>1.35±0.01</td>
<td>22.3 mM</td>
<td>5</td>
</tr>
<tr>
<td>NE 10⁻⁵M</td>
<td>2.0±0.22</td>
<td>2.1±0.22</td>
<td>-6.39±0.11</td>
<td>4.1x10⁻³ M</td>
<td>-6.50±0.04</td>
<td>3.2x10⁻³ M</td>
<td>5</td>
</tr>
<tr>
<td>HI 10⁻⁴M</td>
<td>2.5±0.26</td>
<td>2.7±0.29</td>
<td>-5.92±0.10</td>
<td>1.2x10⁻⁴ M</td>
<td>-5.88±0.08</td>
<td>1.3x10⁻⁴ M</td>
<td>5</td>
</tr>
<tr>
<td>CaCl₂ *</td>
<td>2.7±0.15</td>
<td>2.9±0.38</td>
<td>-3.89±0.04</td>
<td>0.13 mM</td>
<td>-3.81±0.09</td>
<td>0.15 mM</td>
<td>5</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n, number of animals; [A], agonist concentration; DOCA, deoxycorticosterone acetate-induced hypertensive swine; KCl, elevated potassium; NE, norepinephrine; HI, histamine; CaCl₂, external calcium in K⁺-depolarized tissues.

*Concentrations of calcium giving maximal responses varied between 1.6 and 10 mM.

EC₅₀ between groups (Table 3). Maximal stresses induced by each agonist were not altered by treatment. Stresses developed by treated and untreated preparations can be compared directly since the fraction of cells in each strip was the same (Table 2). In an attempt to maximize stress, 10⁻⁵ M norepinephrine was added to K⁺-PSS solution. This increased force development in both control and hypertensive vessels by less than 1.08 times the stress produced by K⁺-PSS alone.

Dynamic Characteristics

The time course of the isotonic shortening response at an afterload of 0.1 Sₒ was measured in six hypertensive vessels, contracted in K⁺-PSS. This is a measurement that provides an assessment of the rate of activation, the time course of cross-bridge phosphorylation, and of crossbridge cycling rates. These experiments required up to 9 hours so hypertensive tissues could not be compared with controls shipped at the same time with only one lever apparatus. Due to the limited number of viable tissues, we elected to study the hypertensive preparations and compare the results with carotid preparations obtained at slaughter in Virginia. Virginia controls yielded isometric responses (2.9±0.2x10⁵ N/m², n=8) that were comparable to the Michigan controls. The isotonic experiments were performed by using thin strips of media. These generally develop less stress due to surface cell damage, but allow greater resolution of mechanical events due to minimized agonist diffusional delays.

The results obtained on vessels from DOCA-induced hypertensive swine were qualitatively similar to those seen in thin strips of normal swine carotid media obtained in Virginia. However, the shortening responses of hypertensive vessels were more variable than seen in normal control vessels. In four cases the peak velocity occurred 20-25 seconds after addition of K⁺-PSS and in two cases at 10 seconds. These values bracket a control average of 12-15 seconds. A major determinant of

FIGURE 3. Line graphs showing concentration-response curves to elevated potassium (KCl) (panel A), norepinephrine (panel B), external calcium (CaCl₂) in K⁺-depolarized tissues (panel C), and histamine (panel D). Fractional response is calculated as active stress elicited by the agonist. Mean±SEM are shown for vessels from control (○) and hypertensive (●) animals (all from Michigan). Number of animals for each curve is given in Table 3.
the time to peak velocity is strip thickness and therefore, agonist diffusion times. Since the media was thicker in the hypertensive carotid vessels, "thin tissues" prepared from this group might also tend to be thicker and show a slower response due to longer K+ diffusional paths. Velocity time courses of two individual muscle strips matched for stress development are shown in Figure 4. In hypertensive strips, mean values of shortening velocity fell from a peak of 0.026±0.002 to 0.012±0.001 L/sec after 8 minutes of stimulation. A similar ratio (2.25) of peak/8 minutes velocity was measured in control carotid vessels.

Discussion

The results of this study provide information directly relevant to the DOCA-induced alterations in the carotid media. However, the experimental approach was designed to address a more general question. Are changes in the contractile apparatus of vascular smooth muscle necessarily associated with medial thickening? This aim required an experimental preparation in which cellular contractile function could be estimated. The swine carotid media preparation is particularly favorable for biomechanical characterization since tissues can be obtained with a uniform geometry in which the cells are aligned in the axis of the mechanical measurements. Detailed studies on this tissue indicate that appropriately normalized estimates of tissue force, length, or velocity yield values applicable to cellular function. These properties have been exploited by many laboratories, making this perhaps the best characterized smooth muscle preparation available with respect to contractile system function and its regulatory mechanisms. The availability of carotid arteries from hypertensive swine provided an opportunity to address the general question stated above.

This model placed constraints on the work. Only one carotid artery from a control and a hypertensive pig was available for each experiment at intervals of 1–3 months and there were unanticipated problems causing loss of some vessels. The study was initiated with a set of viability criteria based on reactivity to depolarization and on comparison with mechanical output obtained with swine carotid arteries studied up to 3 days after collection in Virginia. In practice, locally collected and air expressed tissue could not be distinguished, and all viable arteries from Michigan were included in data tabulations. The unidentified factor producing tissue destruction was apparently both catastrophic and episodic.

The force-generating capacity provides one index of contractile system function. This parameter depends on a number of variables that include the cross-sectional area of the tissue, the fraction occupied by smooth muscle cells, force-length relation, and the level of activation achieved in response to a specific stimulus. All of these may potentially change in hypertension. The force-generating capacity for a given stimulus can be compared in this preparation when force is measured at L₀ and normalized as a cellular stress: force/cross-sectional area x fraction of the cross section occupied by smooth muscle cells.

Most (perhaps all) stimuli fail to maximally activate vascular smooth muscle in vitro, and there are many documented instances of changes in sensitivity to physiologically important vasoactive substances in hypertension. Our approach to assuring comparability in activation was to examine the response to a number of stimuli capable of inducing high stresses. Norepinephrine acts by mobilizing cellular Ca compartments, while the response to K+ depolarization is dependent on influx of extracellular Ca. Histamine and CaCl₂ with depolarized preparations were previously found to produce the highest active cellular stress in the carotid media that have been reported for a smooth muscle. No differences were found in the dose-response relations or in maximal stresses between control and
DOCA-treated tissues in response to any of these agents that act via both receptor-operated and potential-dependent mechanisms to mobilize various Ca^{2+} pools. This result provides considerable assurance that comparable levels of activation were attained. These findings are consistent with previous results demonstrating that, when compared at the same length, the agonist sensitivity of vessels from hypertensive animals was different from controls.26 Maximal cellular stress-generating capacities were the same in both the control and hypertrophic carotid media preparations and exceed $6 \times 10^5$ N/m$^2$ after correcting the tissue stress values (Table 3) for the cell fraction of the tissue (Table 2). This value is about twice the stress developed by a tetanized skeletal muscle cell and strongly suggests that tissue viability was not impaired.

The findings with respect to active stress development imply that there was no quantitative change in the number of crossbridges generating force additively in the hypertrophic preparation nor in the nature of that interaction. However, crossbridge cycling rates and the dynamic behavior of the tissue might change.11 Shortening velocities in general depend on the same variables that influence force plus the isoenzymatic form of myosin and the level of myosin phosphorylation in smooth muscle.16,27 The tissue supply was too limited to undertake an extensive determination of stress-velocity curves at various levels of phosphorylation. However, data from one such experiment (not shown) fell close to the regression line for $V_o$ (the maximum shortening velocity at zero external load obtained from a stress-velocity curve) on myosin phosphorylation in K+-stimulated control tissues (see Figure 5 in Reference 28). The time course of active stress development and of isotonic shortening velocity at a low, constant afterload were comparable in K+-depolarized control and hypertrophic tissues (Figure 4). These velocity transients were associated with transients in crossbridge phosphorylation27,28; moreover, agonist-induced transients in myoplasmic Ca^{2+} concentration appear to be the primary basis for changes in phosphorylation and velocity in this preparation.16,27 Since K+ appeared to produce comparable cellular activation in the hypertrophic preparation, the data suggest that the dynamics of contraction were unaltered from those of control tissues.

In summary, DOCA-induced hypertension in the swine was associated with marked medial thickening amounting to an 80% increase in medial thickness. The increases in smooth muscle and passive elastic elements were proportional, with no change in cell fraction or passive stresses. While the enlarged preparations could generate considerably higher forces, active stresses and indexes of crossbridge dynamics did not change. We conclude that the characteristics of the contractile apparatus and the Ca^{2+}-dependent regulatory mechanisms were not altered in the carotid smooth muscle cells of the hypertensive animal. This conclusion is valid only for this model.

A few studies generally meeting the criteria that must be satisfied for this type of analysis have been done with arteries from the spontaneously hypertensive rat. In these reports, maximum active stresses at $L_o$ were comparable in mesenteric, aortic, and carotid arteries from spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) control rats. Similarly, various estimates of shortening velocities in matched contractions with aortas, portal veins, and mesenteric arteries from SHR and WKY controls did not differ. On balance, these data suggest that the hypertrophic response associated with hypertension can occur in the absence of altered properties of the contractile apparatus. The cited literature represents a minority of observations, and impaired stress development is commonly reported for in vitro arterial preparations from hypertensive animals (References 12 and 31 are of particular interest as careful studies in which some vessels exhibited changes while others did not). Alterations in extent of shortening and maximal velocity of shortening have also been reported.32,36 Such observations may reflect changes unique to some models or vascular beds, may reflect altered reactivity to the agonist employed, may represent instances in which additional factors in a complex process are revealed, or may simply illustrate the difficulties of assessing contractile system capacity for complex tissues in absolute terms.

The DOCA model of hypertension results in significant thickening of the carotid media. The sizable increase in medial thickness was associated with thickening of lamellae without significant changes in their number. A similar pattern was described for aortas from DOCA-induced hypertensive rats.37 Medial hypertrophy in the SHR model has been reported to result from both cellular proliferation and cellular hypertrophy, depending on vessel size and animal age. Our results indicate only an enlarged muscle mass of an elastic artery of the DOCA hypertensive model and do not exclude the possibility that other arterial vessels may have undergone alterations of a different nature. A reasonable hypothesis is that the hypertrophic response of the media observed in this study is adaptive to maintain a certain range of wall stresses with a quantitative increase in cytoskeletal, myofibrillar, and extracellular connective tissue proteins.

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