Summary  The purpose of this study was to determine if any changes occurred in the basal and stimulated rates of oxygen consumption and lactate production of thoracic aortas from spontaneously hypertensive rats (SHR) and renal and deoxycorticosterone acetate (DOCA)-salt hypertensive rats, and, if so, whether these changes were similar in these three models of hypertension. Rings of thoracic aorta were placed in an isothermic (37°C) muscle bath, and isometric tension development, oxygen consumption, and lactate production were measured. The results indicated that under basal conditions oxygen consumption, but not lactate production, was higher in aortas from all three hypertensive models; the elevation above control was greatest in the renal model (95%) and smallest in SHR (34%). On stimulation with 60 mM KCl, a significant increase in oxygen consumption above basal value occurred in all aorta samples (p < 0.05); however, lactate production was increased above basal only in aortas from hypertensive animals. Only in aortas from renal and DOCA-salt models was the rate of oxygen consumption during stimulation significantly greater than that of their normotensive controls (p < 0.05). Developed active stress in response to KCl was the same in all groups, and when the change in lactate production or oxygen consumption was expressed relative to the amount of active stress developed, no differences were observed. These results suggest that 1) compared to values in aortas from normotensive animals, only the basal rate of oxygen consumption is higher; 2) this higher level of basal metabolic activity is not associated with an alteration in the metabolic cost of force development; and 3) there are quantitative differences between the models with regard to their metabolic characteristics. (Hypertension 8: 103-108, 1986)
pared with aortas from normotensive rats, aortas from both models exhibited an elevated basal rate of oxygen consumption, which confirms the earlier work of Daly and Gambetta-Gurpide; however, the elevation was much greater in the aldosterone-salt model. During tension development in response to elevated extracellular K+, oxygen consumption increased relative to basal values in both models; however, only in aortas from aldosterone-salt treated rats was the rate of consumption during stimulation greater than that of the normotensive control. Lactate production was observed to decrease during tension development in aortas from SHR and to increase in aortas from aldosterone-salt-treated rats. Because of potential methodological differences between these two studies, it is not clear if the observed differences in the metabolic characteristics of vessels from these two forms of hypertension reflect differences in tissue response to these two models of hypertension.

The literature is replete with observations suggesting that aortas from SHR and from renal and mineralocorticoid hypertensive rats undergo similar changes. Ion flux data suggest that an elevation in Na+-K+ pump activity occurs in these three models. Paul and colleagues have suggested that in a variety of vessels increases in lactate production occur under conditions known to stimulate sarcolemmal Na+-K+ pump activity. Since Na+-K+ pump activity has been shown to be elevated in these hypertensive models, an elevated lactate production is expected. In addition, it has been demonstrated that thoracic aortas from these three hypertensive models have an increased contractile and connective tissue protein content, which may result in an alteration in the relationship between the magnitude of energy use and the magnitude of tension development.

The present study attempted to compare, under identical conditions, the oxygen consumption and lactate production of thoracic aortas from SHR, renal hypertensive rats, and DOCA-salt hypertensive rats during basal and stimulated (KCl) conditions to determine if metabolic alterations occurred in association with hypertension and if there were differences in metabolic changes between these models.

Materials and Methods

Animal Models

Male Wistar Kyoto rats (WKY) and SHR were obtained from Taconic Farms (Germantown, NY, USA). One group of WKY served as age-matched controls for the SHR. These were killed at 14 to 15 weeks of age, approximately 8 to 9 weeks after the development of hypertension in the SHR. Other WKY were used to prepare renal and DOCA-salt models of hypertension as well as their respective controls.

Renal hypertension was induced by placing a silver clip (inside diameter, 1 mm) around one renal artery of 5- to 6-week-old WKY and removing the contralateral kidney 1 week later. Age-matched control animals were exposed to the same surgical manipulation, except the clip (inside diameter, 1 mm) did not produce stenosis. Two to 5 weeks after the establishment of hypertension (at 7-11 weeks of age), the animals were killed by decapitation and their aortas studied as described below. The DOCA-salt hypertension was produced in 4- to 5-week-old WKY by removing one kidney and giving weekly subcutaneous injections of deoxycorticosterone pivalate (40 µg/100 g body weight; Ciba Pharmaceuticals, Summit, NJ, USA). The rats drank only water containing 0.9% NaCl and 0.2% KCl. Control WKY were not given subcutaneous injections and were allowed to drink normal tap water. Four to 5 weeks after the establishment of hypertension (at 8-10 weeks of age), the rats were killed by decapitation and their aortas were studied as described below.

Blood pressure was measured by the tail cuff method in all rats, and at least five determinations were made on each rat on a given day and averaged to serve as the blood pressure of the animals at that time. During the developmental stage of hypertension, blood pressure was measured three times a week. A systolic blood pressure of 150 mm Hg or higher was the criterion for hypertension. When the animals were killed, their body weights were determined.

Metabolism Bath

The isothermic muscle bath used in these experiments was similar to that described by Paul and Peterson. It consisted of a 3.5-ml glass chamber with a polarographic oxygen electrode (model 5331; Yellow Springs, OH, USA) incorporated into its side. The chamber was effectively sealed from the atmosphere by a stainless steel plug (40 mm long) containing two holes (inside diameter, 2 mm) used to remove the bath contents and to connect the arterial segment to a Statham force transducer (Oxnard, CA, USA). Incorporated into the base of the chamber was a glass-encased magnetic stirring bar for continuous mixing of the bath contents.

The muscle bath was connected through a short length of tubing and a stopcock to a preheated reservoir (37°C) containing a physiological salt solution (PSS) of the following composition (in mM): NaCl, 132; KCl, 4.7; NaHCO3, 18; MgSO4·7H2O, 1.2; CaCl2, 2.0; glucose, 5. This solution was continuously bubbled with 5% CO2, 95% air, which maintained the pH at 7.4 and the oxygen content at 182 nmol/ml, assuming a solubility of oxygen in water of 0.0243 ml/ml and a partial pressure of oxygen in the gas of 19%. This amount of oxygen is sufficient to maintain a maximum contraction for up to 2 hours. Solution from the reservoir could be allowed to flow into the bottom of the muscle bath and out through the holes in the stainless steel plug by manipulating the stopcock. In this way, fresh PSS or PSS containing 60 mM added KCl could be introduced into the bath. Each time the bath was flushed with fresh solution it was rinsed three times, and each rinse was at least 20 ml in volume.

The output of the oxygen electrode and force transducer was displayed on a Brush strip chart recorder.
(Cleveland, OH, USA). At the beginning and end of each experiment, the oxygen consumption of the electrode was determined and the average for that given experiment used to correct the consumption measured in the presence of tissue. The electrode oxygen consumption averaged 10% of that consumed by tissue.

**Metabolic and Contractile Characterization**

Immediately after the aorta had been removed from the animal, it was placed in PSS at room temperature; adhering fat was removed, and a segment 5 to 7 mm long was cut 1 cm below the branch of the subclavian artery. The segment was mounted in the metabolism bath within 15 to 20 minutes after removal from the animal.

The muscle segment was threaded onto two stainless steel rods (23 gauge); one was permanently fixed to the stainless steel plug, and the second, which passed through the plug, was connected by a movable stage micrometer to the force transducer. Immediately after the segment was placed within the chamber, the chamber was filled with PSS and the unstretched length of the segment was determined by moving the rod attached to the force transducer. The distance, as indicated by the micrometer, between the fixed and movable rods at which tension was first detected was designated as the unstretched length. The segments were then stretched until a stable force of 20 mN had been applied. This level of resting tension resulted in a strain of 0.91 ± 0.06 (n = 67), which was not significantly different between the various groups.

Since it has been shown that the active stress-strain properties of vessels from these three models of hypertension are similar to that of normotensive vessels, \[ \frac{\text{oxygen consumption}}{\text{lactate production}} \] comparing the vessels at a similar strain presumably placed them at the same position on their active length-tension curves. No aorta from the three hypertensive models demonstrated spontaneous contractile activity. This observation, combined with the fact that a 20-mN tension produced a similar strain in all vessels, suggests a minimal and similar level of basal active tension in all preparations.

Fresh PSS was again washed into the chamber, and oxygen consumption was monitored. Although the period of monitoring was timed, it varied between 30 and 45 minutes to allow sufficient lactate to accumulate in the solution bathing the muscle for accurate determination. At the end of a given period, the contents of the bath were removed by a syringe through one of the holes in the stainless steel plug and fresh PSS from the reservoir was allowed to flush the chamber. The bath contents that were removed were frozen for later determination of total lactate content. Three basal oxygen and lactate determinations were made before the muscle was stimulated to contract. Immediately on adding PSS containing an additional 60 mM KCl, oxygen consumption and lactate production were followed for 30 to 45 minutes during the contraction. A constant level of contractile tension was maintained in all tissues studied. After a KCl-induced contraction, two additional basal periods were measured. These two periods were averaged with the first three and used as the basal oxygen consumption and lactate production for the particular tissue. There were no systematic differences in oxygen and lactate values between these five basal periods.

After all measurements had been performed, the tissues were removed from the chamber and blotted and their wet weights determined. The tissue cross-sectional area was calculated at the length at which active tension was measured from the relationship between wet weight, length (l), and density (D): wet weight/(l × D), where D equals 1.05 g/cm³. Lactate was measured fluorometrically as the formation of the reduced form of nicotinamide adenine dinucleotide (NADH) by converting the lactate to pyruvate through the action of lactate dehydrogenase in the presence of phosphoenol pyruvate, phenylhydrazine (pH 9), and nicotinamide adenine dinucleotide (NAD; Sigma Chemical, St Louis, MO, USA). Oxygen consumption and lactate production were expressed in terms of nanomoles per minute per gram of wet weight, while force developed was expressed in terms of Newtons per wall cross-sectional area (stress).

**Statistical Analysis**

The data were statistically analyzed in the following ways. The Wilcoxon signed ranks test for related samples was used to compare the value of a given parameter before and after the initiation of contraction with KCl. Student's t test was used to compare a given parameter between a hypertensive group and its normotensive control, while analysis of variance was used to compare a given parameter between hypertensive groups. To compare any two groups, a modified t test was performed in which the within-group mean square from the analysis of variance table was used to calculate t, as described by Wallenstein et al.

**Results**

Table 1 shows the body weights and systolic blood pressures of the animals as well as the calculated cross-sectional area of the vessel rings at the length at which force was measured. None of the body weights of the hypertensive animals differed significantly from those of their controls; however, all hypertensive animals had a significantly elevated systolic blood pressure, which was highest in the DOCA-salt animals. None of the cross-sectional areas were significantly elevated in the hypertensive groups relative to those of their controls.

Table 2 compares the oxygen consumption and lactate production of aortas from various animal groups under basal conditions. Aortas from all three hypertensive models had a significantly higher oxygen consumption than their respective controls; however, none had elevated lactate production. When the three hypertensive models were compared, basal oxygen consumption was most elevated in the renal model (95%) and least elevated in SHR (34%).

In association with contraction induced by 60 mM
KCl, oxygen consumption increased significantly above basal levels in aortas from all animal groups studied; however, lactate production increased significantly above basal values only in aortas from hypertensive animals (Table 3). Compared with control values during stimulation, the oxygen consumption of aortas from renal and DOCA-salt models, but not SHR, was significantly elevated. All vessels from hypertensive animals developed the same level of active stress relative to that in their controls. To obtain an estimate of the metabolic cost of maintaining this level of active stress, the change in oxygen consumption and lactate production with contraction was expressed as a function of the level of active stress. This comparison indicated no significant differences between aortas from normotensive and hypertensive animals.

### Discussion

The results of the present study confirmed previous reports\(^1\) that hypertension is associated with an increase in the basal metabolic activity of aortas and indicated that, under similar conditions, oxygen consumption but not lactate production was elevated in SHR and renal and DOCA-salt hypertensive models. In addition, the data indicated that quantitative differences in basal oxygen consumption existed between these three hypertensive models (see Table 2). Oxygen consumption was highest in aortas from renal hypertensive rats (95%), while aortas from SHR showed the smallest elevation (34%) and those from DOCA-salt animals showed an intermediate increase (51%). These findings are in accord with the suggestion of McMahon and Paul\(^4\) that mineralocorticoid-salt hypertension is associated with a larger increase in basal oxygen consumption than is genetic hypertension.\(^3\)

Stimulation with KCl, vessels from normotensive and hypertensive rats exhibited an increase in oxygen consumption above basal values, but only the aortas from hypertensive animals exhibited an elevation in lactate production relative to basal values (see Table 3). These changes in lactate production during stimulation are different from those observed by others. McMahon and Paul\(^4\) reported an increase in lactate production with KCl stimulation in aortas from both control and aldosterone-salt hypertensive rats, but Amer and Hellstrand\(^5\) reported a decrease during stimulation of aortas from both control and SHR. Although the reasons for these observational discrepancies are

### Table 1. Weight, Blood Pressure, and Aortic Cross-Sectional Area of the Hypertensive and Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Body wt (g)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Cross-sectional area (mm(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>265 ± 21 (17)</td>
<td>182 ± 4* (18)</td>
<td>2.4 ± 0.3 (17)</td>
</tr>
<tr>
<td>Control</td>
<td>238 ± 21 (14)</td>
<td>132 ± 4 (14)</td>
<td>2.6 ± 0.4 (12)</td>
</tr>
<tr>
<td>Renal hypertensive</td>
<td>266 ± 18 (12)</td>
<td>178 ± 5* (12)</td>
<td>2.2 ± 0.4 (12)</td>
</tr>
<tr>
<td>Control</td>
<td>240 ± 12 (11)</td>
<td>131 ± 2 (11)</td>
<td>1.6 ± 0.1 (11)</td>
</tr>
<tr>
<td>DOCA-salt hypertensive</td>
<td>204 ± 18 (6)</td>
<td>217 ± 9* (6)</td>
<td>4.8 ± 0.4 (6)</td>
</tr>
<tr>
<td>Control</td>
<td>256 ± 18 (6)</td>
<td>132 ± 2 (6)</td>
<td>3.8 ± 0.6 (6)</td>
</tr>
</tbody>
</table>

All values are means ± SEM; the number of observations is in parentheses. *p < 0.05, relative to control values; \(p < 0.05\), relative to SHR and renal hypertensive rats.

### Table 2. Basal Metabolic Characteristics of Aortas from the Hypertensive and Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>(O_2) consumption (nmol/min/g wet wt)</th>
<th>Lactate production (nmol/min/g wet wt)</th>
<th>(P) (mN/mm(^2))</th>
<th>(\Delta O_2) production/P*</th>
<th>(\Delta) lactate production/P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>436 ± 31* (18)</td>
<td>77 ± 17* (17)</td>
<td>13 ± 2 (18)</td>
<td>16 ± 2 (18)</td>
<td>1.8 ± 0.9 (17)</td>
</tr>
<tr>
<td>Control</td>
<td>369 ± 35* (14)</td>
<td>56 ± 14 (13)</td>
<td>13 ± 2 (14)</td>
<td>12 ± 2 (14)</td>
<td>0.5 ± 0.4 (13)</td>
</tr>
<tr>
<td>Renal hypertensive</td>
<td>510 ± 50* (12)</td>
<td>18 ± 2* (12)</td>
<td>21 ± 3 (12)</td>
<td>9 ± 2 (12)</td>
<td>0.3 ± 0.1 (12)</td>
</tr>
<tr>
<td>Control</td>
<td>354 ± 38* (11)</td>
<td>22 ± 1 (11)</td>
<td>21 ± 3 (12)</td>
<td>10 ± 2 (11)</td>
<td>0.1 ± 0.1 (11)</td>
</tr>
<tr>
<td>DOCA-salt hypertensive</td>
<td>567 ± 18* (6)</td>
<td>80 ± 16* (6)</td>
<td>12 ± 1 (6)</td>
<td>19 ± 7 (6)</td>
<td>2.7 ± 0.8 (6)</td>
</tr>
<tr>
<td>Control</td>
<td>453 ± 15* (6)</td>
<td>58 ± 12 (6)</td>
<td>12 ± 2 (6)</td>
<td>17 ± 3 (6)</td>
<td>1.2 ± 0.6 (6)</td>
</tr>
</tbody>
</table>

All values are means ± SEM; the number of observations is in parentheses. *p < 0.05, relative to control values. \(p < 0.05\), relative to values in controls stimulated with KCl.

### Table 3. Metabolic and Contractile Characteristics during KCl Stimulation of Aortas from Hypertensive and Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>(O_2) consumption (nmol/min/g wet wt)</th>
<th>Lactate production (nmol/min/g wet wt)</th>
<th>(P) (mN/mm(^2))</th>
<th>(\Delta O_2) production/P*</th>
<th>(\Delta) lactate production/P*</th>
</tr>
</thead>
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<tr>
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<td>17 ± 3 (6)</td>
<td>1.2 ± 0.6 (6)</td>
</tr>
</tbody>
</table>

All values are means ± SEM; the number of observations is in parentheses. *p = contraction. \(\Delta\) Measured as (nmol/min/g wet weight)/(mN/mm\(^2\)). \(\Delta p < 0.05\), relative to basal value; \(\Delta p < 0.05\), relative to values in controls stimulated with KCl.
unknown, one possibility may be the strain of rat used. In a preliminary study, we reported an increase in lactate production following KCl stimulation using normotensive Wistar rats,22 while we did not observe a change in the current study using normotensive WKY.

During stimulation, the aortas from the renal hypertensive model again had the highest oxygen consumption relative to that of controls (45%), while the aortas from SHR had the smallest (18%) and those from DOCA-salt hypertensive rats had an intermediate (25%) consumption. When the change in oxygen consumption or lactate production was expressed as a function of the amount of active stress developed, no change with hypertension was observed. This suggests that even though there are alterations in basal metabolic rate associated with the development of hypertension, the changes do not affect the metabolic cost of developing force and the energy consumption by the contractile proteins is not altered. Since it has been shown that the net production of contractile proteins increases in these hypertensive models,10-11 an unchanging metabolic cost of force development suggests that these newly synthesized proteins are unaltered. Similar conclusions were reached by Arner and Hellström3 and McMahon and Paul.2

The reason for the higher basal oxygen consumption in aortas from hypertensive rats is unknown. Since only basal oxygen consumption was elevated in all hypertensive models, it cannot be explained by an elevation in the proportion of muscle cells. As aortas from all three models are known to increase their net protein production,15-17 the elevated oxygen consumption may be required for this higher synthetic activity. In addition, these models have been shown to have an elevated Na+-K+ pump activity,5 which would also create a greater metabolic demand. Paul and co-workers9 and Kutchai and Geddis20 have suggested that the source of ATP for the sarcolemmal Na+-K+ pump is derived from aerobic glycolysis (lactate formation in the presence of oxygen); thus, a higher Na+-K+ pump activity would be expected to be reflected in a higher lactate production. It is interesting that none of the aortas from the hypertensive models exhibited an elevated basal lactate production, even though they are all reported to have an elevated Na+-K+ pump activity (see Table 2). They were, however, the only tissues to undergo a significant increase in lactate production on stimulation with KCl.

An increase in extracellular K+ stimulates the Na+-K+ pump through activation at its extracellular binding site as well as by a depolarization-induced Na+ gating, which results in an increase in activation by Na+ at its intracellular binding site. The observation that only aortas from hypertensive animals increased their lactate production during KCl stimulation suggests that the Na+-K+ pump is activated to a greater extent by the effects of elevated extracellular K+ in vessels from hypertensive animals. This is in agreement with studies using K+-induced relaxation as an indicator of Na+-K+ pump activity. Vessels from DOCA-salt hypertensive rats24 and SHR25 were more responsive to the relaxant effects of elevated extracellular K+.

The reason for the differences in metabolic characteristics between different models of hypertension is also unknown. Since the etiology of hypertension is different in each model, some unique aspect of the etiology of each may be responsible. Alternatively, a stimulus common to all models, such as elevated transmural pressure, may initiate different cellular responses because of differences between the various models in the age at onset of hypertension, rate of blood pressure elevation, duration of the hypertension, or the level of hypertension achieved.28 Renal and DOCA-salt models undergo rapid increases in systolic blood pressure relative to those seen in SHR. Hypertension in the renal and DOCA-salt models used in this study was initiated at the same age (4–6 weeks) and maintained for a similar period; however, the DOCA-salt model achieved a higher systolic blood pressure (see Table 1). The observation that aortas from renal hypertensive rats achieved the greatest increase in oxygen consumption relative to that of controls, while its final blood pressure level was not the highest, suggests that the magnitude of blood pressure change may not be the sole determinant of the metabolic characteristics. In the DOCA-salt model, many changes in vessel properties have been attributed to DOCA alone26-29 rather than to the elevation of systolic pressure; therefore, some of the metabolic changes in this model may be due to DOCA. However, McMahon and Paul4 observed no effect of aldosterone on vessel metabolism.

Even though aortas from various hypertensive models have been reported to have similar characteristics (e.g., increased protein content, increased contractile reactivity, increased Na+-K+ pump activity) when compared with aortas from normotensive animals, our results indicate that they differ in their metabolic characteristics, which may depend on the unique etiology of the particular form of hypertension.

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