Cardiac Contractile and Coronary Flow Reserves in Deoxycorticosterone Acetate–Salt Hypertensive Rats

Jin Yamamoto, Masayuki Tsuchiya, Muneyasu Saito, and Masao Ikeda

SUMMARY Cardiac contractility and coronary flow were compared in conscious rats with established deoxycorticosterone acetate–salt hypertension and in those with sham treatment. The hypertensive rats showed a 32% increase in left ventricular/body weight ratio at 9 weeks of treatment and 42% at 18 weeks of treatment. Resting peak rate of change of pressure ($dp/dt$) was unchanged at 9 weeks and increased at 18 weeks in hypertensive rats, while isoproterenol-stimulated maximal, propranolol-induced minimal, and $Ca^{2+}$-stimulated maximal peak $dp/dt$ were greater at 18 weeks. These data indicate the preservation of contractile function. At 18 weeks, the $\beta$-adrenergic receptor-mediated contractile reserve, estimated from isoproterenol-stimulated maximal and resting peak $dp/dt$, was reduced but the propranolol-induced decrease in peak $dp/dt$ was increased in hypertensive rats compared with sham-treated rats. Thus, at this stage, a greater portion of the total contractile capacity appeared to be mobilized with prolongation of hypertension and progression of left ventricular hypertrophy. No differences were observed in left ventricular and right ventricular coronary flow (microspheres) and left ventricular inner/outer flow ratio at rest and with dipyridamole-induced maximal coronary dilatation, at 9 and 18 weeks. There were no alterations in left or right ventricular coronary flow reserves, as estimated from resting and dipyridamole-induced values. The minimal coronary vascular resistance (normalized for gram of tissue) of both the left and right ventricles was increased at either stage, which suggests the occurrence of structural coronary vascular changes. Thus, basal coronary flow and a coronary flow reserve were uncompromised despite evidence of structural coronary vascular alterations in these hypertensive rats. (Hypertension 7: 569–577, 1985)

Key Words • left ventricular hypertrophy • minimal coronary vascular resistance • peak rate of change of pressure ($dp/dt$) • radioactive microspheres • isoproterenol • propranolol • dipyridamole

SYSTEMIC hypertension often leads to alterations in cardiac performance associated with an increase in cardiac mass and coronary circulation. There is still considerable controversy regarding cardiac performance in the presence of hypertension, most of which stems from the wide spectrum of cardiac function caused by variations in the duration, severity, and type of hypertension. Little is known of cardiac function and coronary hemodynamics in deoxycorticosterone acetate (DOCA)–salt hypertension. The literature seems to consist of reports on the unaltered mechanical properties of isolated papillary muscles and the increased intercapillary distance of superficial epicardial muscles. In view of this and earlier data on some features of hemodynamic, neurohumoral, and myocardial and coronary vascular histopathological changes in this form of hypertension, we wanted to assess cardiac function and coronary hemodynamics in DOCA-salt hypertensive rats. Since we were interested in the concept of contractile reserves, features important in comprehending the heart's behavior in the presence of hypertension, measurements were made not only under resting conditions but during inotropic and coronary vasodilator interventions.

The major goals of this study were to evaluate 1) cardiac contractility (positive peak rate of change of pressure [$dp/dt$]) at rest and during maximal left ventricular (LV) activation with inotropic agents and 2) CF at rest and at maximal coronary dilatation with dipyridamole (with consideration toward LV transmural flow distribution) in conscious rats at two estab-
Materials and Methods

Male Wistar rats, initially aged 6 to 7 weeks and weighing 180 to 230 g, were used. One week after the rats had undergone a left nephrectomy, the DOCA-salt treatment, which consisted of weekly subcutaneous injections of 15 mg/kg of DOCA and provision of 1% saline solution as drinking water, was initiated. A second group of rats underwent a left nephrectomy and were then injected with a solvent (sesame oil), given tap water, and used as the controls (sham-treated rats). Food and water were available ad libitum.

Nine and 18 weeks after the start of the treatments, two sets of experiments were performed in both DOCA-salt hypertensive and sham-treated control rats (total number = 104). Body weight was measured just before the rats underwent intravascular cannulation with local use of 1% lidocaine and under general anesthesia using ether.

Experiment I

On the day of the experiment, tip-tapered PE-50 catheters were introduced into the left femoral artery and left jugular vein. A high-fidelity micropipette catheter (PR-247, Millar Instruments, Houston, TX, USA) was positioned in the left ventricle through the right carotid artery. These catheters were secured at each site and brought out between the shoulder blades, and the wounds were closed. Three hours was allowed for the rats to recover from the operation and anesthesia.20

Each rat was placed in a nonconfining small cage. The arterial catheter was attached to a Statham P23ID transducer (Gould Inc., Oxnard, CA, USA) and a polygraph (Model 360, Sannei, Tokyo). Mean arterial pressure (MAP) was recorded with electrical analog integration. The micropipette pressure transducer was connected to a DC amplifier for monitoring LV pressure. Heart rate (HR) was obtained by a tachograph triggered from a LV pressure signal. The rate of change of LV pressure (dp/dt) was derived with an active differentiator. This differentiator with its own calibration circuit was calibrated using a function generator and a reference pressure (MAP) was recorded with electrical analog integration. The microtip pressure transducer was connected to a DC amplifier for monitoring LV pressure. Heart rate (HR) was obtained by a tachograph triggered from a LV pressure signal. The rate of change of LV pressure (dp/dt) was derived with an active differentiator. This differentiator with its own calibration circuit was calibrated using a function generator and a reference pressure.

After determining MAP, HR and peak dp/dt at rest, I-isoproterenol hydrochloride (0.2 mg/ml solution), a β-adrenergic agonist, was infused intravenously through the jugular vein with a Harvard 944D pump (Harvard Apparatus, Inc., Millis, MA, USA) at sequentially incremental dosages of 0.04, 0.08, and 0.16 μg/kg/min for every 5-minute period, and the responses during the last minute of each infusion were assessed. Preliminary experiments showed that the peak dp/dt reached a plateau with a dose of 0.08 μg/kg/min and then declined in both DOCA-salt and sham-treated groups. After a 20-minute period of recovery, the responses to graded doses of Ca 2+ (0.068, 0.136, and 0.272 mEq/kg/min), a direct cardiac muscle stimulant, were similarly measured by infusing calcium gluconate (0.4 mEq Ca 2+/ml solution, 0.17, 0.34, and 0.68 ml/kg/min) into the 18-week groups of DOCA-salt and sham-treated rats. The difference between resting and maximal peak dp/dt (Δdp/dt) was taken as the LV contractile reserve.5, 6, 8

In additional groups of the 18-week DOCA-salt and sham-treated rats, the effects of β-adrenergic blockade on peak dp/dt and hemodynamics were determined in an attempt to assess a β-adrenergic component of the resting cardiac contractility. β-Blockade was produced by a bolus intravenous injection of 2 mg/kg of propranolol hydrochloride (1 mg/ml solution).21 Elevation in the HR was prevented by a prior bolus injection of isoproterenol (2 μg i.v.). Doubling the dose had no further effect on the peak dp/dt.

On completion of all the experiments except that using the β-blocker, the rats were exsanguinated, the heart extirpated, the atria and great vessels removed, and the free wall of the right ventricle dissected from the left ventricle. The left ventricle including the septum and the RV free wall were weighed separately.

Experiment II

The preparation of the rats and the determination of cardiac output and CF were as described.22 The evening before the experiment tip-tapered PE-50 catheters were placed in the femoral artery and vein and in the left ventricle through the right carotid artery in ether-anesthetized rats. The next morning, after a 14- to 15-hour recovery period, the rats underwent the same procedures used in the first experiment except that LV pressure was monitored through a fluid-filled catheter and a Statham transducer. Heparin (200 U) was then given intravenously.

Cardiac output and CF were measured with serial injections of radioactive microspheres (15 μ in diameter, labeled with 85Sr, 51Cr, or 141Ce; Minnesota Mining and Manufacturing Co., St. Paul, MN, USA, or New England Nuclear, Boston, MA, USA). After vigorous agitation, 50,000 to 100,000 microspheres, suspended in 0.05 ml of physiological saline, were injected into the left ventricle and flushed with 0.4 ml of freshly drawn donor blood during a 20-second period. Beginning 10 seconds before microsphere injection and continuing for 50 seconds, a reference blood sample was withdrawn with a pump through the femoral arterial catheter at a rate of 0.93 ml/min. Volume loss was immediately restored by injecting donor blood.

After hemodynamic variables were determined and microspheres were injected at rest, each rat was left alone for 20 minutes to promote restabilization. To produce coronary vasodilatation 2 mg/kg/min of dipi-
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or normalized flow (ml/min/g) and given in total (mm calculated by dividing MAP by either total flow (ml/min) per kilogram of body weight and CF as milliliters per minute per gram of wet tissue. The LV inner/outer weight ratio, which we used as an index of LV mass and hence the degree of LV hypertrophy, was increased in the DOCA-salt rats by 32% at 9 weeks and 42% at 18 weeks (p < 0.01) compared with matched controls. In contrast, the RV weight did not differ in either absolute or body-weight-related terms.

Experiment 1

The main data from Experiment I are summarized in Table 2. Compared with the sham-treated rats at rest, the DOCA-salt rats showed significant 39 and 41% increases in MAP with no changes in HR at 9 and 18 weeks respectively (p < 0.05). Resting peak dp/dt was not different at 9 weeks but was significantly greater in the DOCA-salt at 19 weeks (5868 ± 152 vs 4787 ± 100 mm Hg/sec in control rats; p < 0.05).

With incremental doses of isoproterenol, the peak dp/dt increased and reached a plateau at 0.08 μg/kg/p.

| Table 1. Heart Weights in Deoxycorticosterone Acetate (DOCA)-Salt Hypertensive and Sham-Treated Rats After 9 and 18 Weeks of Treatment |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Weight                         | DOCA (n = 20)   | DOCA (n = 24)   | Sham (n = 20)   | Sham (n = 24)   |
| BW (g)                         | 378 ± 8*       | 402 ± 8†       | 411 ± 7         | 460 ± 7         |
| Left ventricle (g)             | 1.07 ± 0.03†   | 1.19 ± 0.03†   | 0.88 ± 0.02     | 0.95 ± 0.02     |
| Left ventricle/BW (g/kg)       | 2.84 ± 0.07†   | 2.96 ± 0.06†   | 2.15 ± 0.05     | 2.08 ± 0.04     |
| Right ventricle (g)            | 0.22 ± 0.01    | 0.24 ± 0.01    | 0.24 ± 0.01     | 0.25 ± 0.01     |
| Right ventricle/BW (g/kg)      | 0.58 ± 0.01    | 0.59 ± 0.02    | 0.57 ± 0.02     | 0.56 ± 0.01     |

Values are mean ± se, and data from Experiments I and II are pooled. Left ventricle weight includes the septum. BW = body weight.
*p < 0.05, †p < 0.01 (compared with respective sham-treated control rats), ‡p < 0.05 (compared with 9-wk DOCA group).
min and later declined in both groups of rats. The HR also reached a plateau with this dose, with no further significant increases; however, MAP fell dose dependently and reached a nadir at 0.16 μg/kg/min. The patterns of the responses were similar in all study groups. Because our primary interest was directed toward assessing maximal peak dp/dt responses to inotropic stimulation, we regarded the peak dp/dt obtained by the dose of 0.08 μg/kg/min as the isoproterenol-induced maximal peak dp/dt (see Table 2).

With this dose of isoproterenol, MAP remained significantly higher in the DOCA-salt groups at either stage (p < 0.01). The HR values were similar among all groups. Peak dp/dt was significantly greater in the 18-week DOCA-salt rats (6591 ± 147 vs 5859 ± 138 mm Hg/sec in control rats; p < 0.05), while there was no difference between the 9-week groups. Interestingly, the isoproterenol-induced maximum increase in peak dp/dt (Δdp/dt) was significantly lower in the 18-week DOCA-salt rats (723 ± 60 vs 1077 ± 88 mm Hg/sec in control rats; p < 0.05), whereas no significant difference was observed between the 9-week groups.

After recovery from isoproterenol, hemodynamic variables and peak dp/dt returned to preinfusion levels in the 18-week DOCA-salt and sham-treated rats (2 rats of each group were omitted because of incomplete recovery; see Table 2).

With incremental doses of Ca²⁺, MAP tended to increase while HR remained unaltered in both groups. Peak dp/dt increased dose dependently in both groups. Doubling the dose from 0.136 to 0.272 mEq/kg/min further increased the peak dp/dt, but this rise was associated with a sudden substantial increase in LV end-diastolic pressure, which presumably was due to effects of fluid rather than Ca²⁺ infusion. In view of the evidence of the high sensitivity of peak dp/dt to short-term increases in preload, we regarded the response to 0.136 mEq/kg/min of Ca²⁺ as maximal (even when using the values at 0.272 mEq/kg/min, the same conclusion was reached). The Ca²⁺-induced maximal peak dp/dt thus obtained was significantly greater in the DOCA-salt rats (p < 0.05; see Table 2). No significant difference was observed in the Ca²⁺-induced maximum increase in peak dp/dt (Δdp/dt) between the DOCA-salt and sham-treated groups. With this dose, MAP did not increase significantly and HR was totally unresponsive in all groups.

In the additional experiment (Table 3), 2 mg/kg of propranolol tended to increase MAP while the HR decreased significantly in the DOCA-salt and sham-treated rats at 18 weeks (p < 0.05). Propranolol significantly decreased the peak dp/dt in both groups (p < 0.05). The propranolol-induced decrease in peak dp/dt (Δ peak dp/dt) was significantly greater in the DOCA-salt group (1850 ± 206 vs 982 ± 190 mm Hg/sec in control rats; p < 0.05). Minimum peak dp/dt during β-blockade was greater in the DOCA-salt group.
TABLE 3. Peak Rate of Change of Pressure (dp/dt) and Hemodynamic Variables at Rest and During β-Blockade with Propranolol in Eight Deoxycorticosterone Acetate (DOCA)-Salt Hypertensive Rats and Eight Sham-Treated Rats After 18 Weeks of Treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Condition</th>
<th>DOCA</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>Rest</td>
<td>466 ± 12</td>
<td>411 ± 10</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>152 ± 3*</td>
<td>103 ± 3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>Rest</td>
<td>164 ± 4*</td>
<td>115 ± 5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>Rest</td>
<td>381 ± 10</td>
<td>371 ± 9</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>321 ± 9†</td>
<td>316 ± 7†</td>
</tr>
<tr>
<td>Peak dp/dt (mm Hg/sec)</td>
<td>Rest</td>
<td>6218 ± 198*</td>
<td>4626 ± 228</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>4368 ± 156*,†</td>
<td>3644 ± 120†</td>
</tr>
<tr>
<td>ΔPeak dp/dt (mm Hg/sec)</td>
<td></td>
<td>1850 ± 206*</td>
<td>982 ± 190</td>
</tr>
</tbody>
</table>

Values are means ± se.

Propranolol was given in a dose of 2 mg/kg i.v.

*p < 0.05 (compared with respective sham-treated control rats), †p < 0.05 (compared with values at rest).

Experiment II

Systemic Hemodynamics

At rest, MAP in the DOCA-salt rats was higher by 47% at 9 weeks and 52% at 18 weeks (p < 0.01; Table 4) than that in the sham-treated rats. Cardiac index and HR were similar in both groups. There were significant increases in total peripheral resistance in the DOCA-salt (vs sham-treated rats) at either stage. During dipyridamol infusion at 2 mg/kg/min, MAP decreased slightly but significantly in all groups (p < 0.05). During dipyridamole infusion MAP remained higher in the DOCA-salt groups. The HR was either unchanged or tended to increase. Cardiac index increased significantly in the 18-week DOCA-salt rats (p < 0.05) and tended to increase in the remaining rats. Total peripheral resistance decreased significantly in the 18-week DOCA-salt group (p < 0.01) and tended to decrease in the other groups. Total peripheral resistance during dipyridamole infusion remained greater in the DOCA-salt groups (p < 0.01 compared with control rats).

Coronary Hemodynamics

At rest there were no significant differences in LV and RV CF or in LV inner/outer flow ratio among any groups (Table 5). Resting total LV CVR (per ventricle) was not significantly different among the groups, while resting normalized LV CVR was significantly greater at 9 and 18 weeks in the DOCA-salt group compared with that in the control group (p < 0.05). Resting total and normalized RV CVR were significantly elevated in the DOCA-salt rats at either time interval (p < 0.05).

Comparison between effects of 2 and 4 mg/kg/min doses of dipyridamole with analysis of variance showed no significant difference in any of the CF and CVR data in the rats studied (data not shown). We therefore considered that the 2 mg/kg/min dose of dipyridamole evoked a maximal coronary dilatation in all groups.

With dipyridamole infusion, LV and RV CF increased more than twofold from resting values; maximal LV and RV CF were comparable among all groups.

TABLE 4. Systemic Hemodynamic Variables at Rest and During Dipyridamole Infusion in 11 Deoxycorticosterone Acetate (DOCA)-Salt Hypertensive and 13 Sham-Treated Rats

<table>
<thead>
<tr>
<th>Variables</th>
<th>Condition</th>
<th>9 wk DOCA</th>
<th>18 wk DOCA</th>
<th>Sham</th>
<th>9 wk DOCA</th>
<th>18 wk DOCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>R</td>
<td>173 ± 3*</td>
<td>180 ± 3</td>
<td>175 ± 3</td>
<td>115 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>160 ± 3†</td>
<td>107 ± 4</td>
<td>158 ± 3*,†</td>
<td>103 ± 3†</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>R</td>
<td>407 ± 13</td>
<td>409 ± 13</td>
<td>407 ± 9</td>
<td>403 ± 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>428 ± 15</td>
<td>410 ± 12</td>
<td>427 ± 12</td>
<td>430 ± 14</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (ml/min/kg)</td>
<td>R</td>
<td>250 ± 14</td>
<td>261 ± 15</td>
<td>248 ± 8</td>
<td>262 ± 12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>273 ± 15</td>
<td>277 ± 14</td>
<td>294 ± 12†</td>
<td>284 ± 9</td>
<td></td>
</tr>
<tr>
<td>TPR (mm Hg/ml/min)</td>
<td>R</td>
<td>1.94 ± 0.09*</td>
<td>1.03 ± 0.06</td>
<td>1.81 ± 0.08*</td>
<td>0.98 ± 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1.67 ± 0.11*</td>
<td>0.94 ± 0.06</td>
<td>1.36 ± 0.04*,†</td>
<td>0.88 ± 0.04</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± se.

R = rest; D = dipyridamole (2 mg/kg/min); TPR = total peripheral resistance.

*p < 0.01 (compared with respective sham-treated control rats), †p < 0.05 (compared with values at rest).
TABLE 5. Coronary Hemodynamic Variables at Rest and During Dipyridamole Infusion in Eight Deoxycorticosterone Acetate (DOCA)-Salt Hypertensive and Eight Sham-Treated Rats

<table>
<thead>
<tr>
<th>Variables</th>
<th>Condition</th>
<th>DOCA</th>
<th>Sham</th>
<th>DOCA</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>9 wk</td>
<td>18 wk</td>
<td>9 wk</td>
<td>18 wk</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF (ml/min/g)</td>
<td>R</td>
<td>4.74±0.52</td>
<td>4.33±0.37</td>
<td>3.99±0.30</td>
<td>4.09±0.42</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>11.0±1.1</td>
<td>10.2±0.84</td>
<td>9.96±0.66</td>
<td>9.53±0.41</td>
</tr>
<tr>
<td>ΔCF (ml/min/g)</td>
<td>D</td>
<td>6.29±0.80</td>
<td>5.88±0.97</td>
<td>5.97±0.53</td>
<td>5.44±0.52</td>
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<tr>
<td>Inner/outer flow ratio</td>
<td>R</td>
<td>1.25±0.52</td>
<td>1.25±0.02</td>
<td>1.18±0.04</td>
<td>1.22±0.03</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1.05±0.06</td>
<td>1.01±0.04</td>
<td>0.93±0.04</td>
<td>1.02±0.05</td>
</tr>
<tr>
<td>Total CVR (mm Hg/ml/min)</td>
<td>R</td>
<td>35.4±5.3</td>
<td>27.2±4.7</td>
<td>35.5±3.3</td>
<td>28.1±2.9</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>14.0±1.5</td>
<td>11.9±1.3</td>
<td>13.2±1.4</td>
<td>11.3±1.3</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/min/g)</td>
<td>R</td>
<td>36.7±5.0*</td>
<td>24.4±3.8</td>
<td>42.6±4.5*</td>
<td>27.5±2.5</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>14.4±1.1*</td>
<td>10.5±0.8</td>
<td>15.8±1.0*</td>
<td>10.8±0.8</td>
</tr>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF (ml/min/g)</td>
<td>R</td>
<td>3.58±0.48</td>
<td>3.75±0.29</td>
<td>3.29±0.38</td>
<td>3.65±0.38</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>8.25±0.94</td>
<td>8.38±1.33</td>
<td>7.32±0.56</td>
<td>8.11±0.65</td>
</tr>
<tr>
<td>ΔCF (ml/min/g)</td>
<td>D</td>
<td>4.67±0.68</td>
<td>4.63±1.04</td>
<td>4.02±0.37</td>
<td>4.46±0.64</td>
</tr>
<tr>
<td>Total CVR (mm Hg/ml/min)</td>
<td>R</td>
<td>232±33*</td>
<td>137±13</td>
<td>228±23*</td>
<td>141±12</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>112±16*</td>
<td>56±9</td>
<td>99±8*</td>
<td>50±6</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/min/g)</td>
<td>R</td>
<td>48.7±4.0*</td>
<td>31.5±2.8</td>
<td>52.4±4.9*</td>
<td>35.5±3.2</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>23.5±3.3*</td>
<td>12.9±2.2</td>
<td>22.8±2.8*</td>
<td>12.5±1.6</td>
</tr>
</tbody>
</table>

Values are means ± SE.
R = rest; D = dipyridamole (2 mg/kg/min); LV = left ventricle; RV = right ventricle; CF = coronary flow; CVR = coronary vascular resistance, given in both total (per ventricle) and normalized (per gram of tissue) terms.
*p < 0.05 (compared with respective sham-treated control rats). All values during dipyridamole infusion are significantly (p < 0.05) different from those at rest.

Discussion

Systemic Hemodynamics and Heart Weight

Experiments I and II show that the increased level of MAP was similar at 9 and 18 weeks, which indicates the presence of established DOCA-salt hypertension. The 15 mg/kg/wk DOCA-salt regimen used in this study did not result in the rapidly progressing malignant hypertension noted in the 30 mg/kg/wk.20,22 Experiment II shows that this hypertension was maintained principally by the increase in total peripheral resistance, with no changes in cardiac output and HR (see Table 4). In this regard, the result confirms and extends our previous observation of the 2- to 8-week DOCA-salt rats.20

Approximately 32 and 42% increases in the LV/body weight ratio were observed at 9 and 18 weeks (see Table 1), compared with matched sham-treated controls, which suggests that in our DOCA-salt rats a moderate degree of LV hypertrophy developed at 9 weeks and progressed further at 18 weeks. On the other hand, the lack of increase in the RV/body weight ratio suggests that the hypertension and the LV hypertrophy did not reach an extreme or a decompensated phase, since increase in this ratio has been observed only in the 18-month-old spontaneous hypertensive rats (SHR).3 Actually, postmortem examination revealed no sign of cardiac failure at either stage.

Resting and Maximal Contractile State

We used the peak LV dp/dt as an index of the cardiac contractile state. Despite some limitations, peak dp/dt has been used to assess short-term and steady state inotropic changes in pathophysiological situations.3,5-11
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The major findings of this part of our study (see Tables 2 and 3) are that, compared with matched controls, in the DOCA-salt rats 1) resting peak dp/dt was unaltered at 9 weeks and increased at 18 weeks; 2) isoproterenol-induced maximal peak dp/dt was normal at 9 weeks and increased at 18 weeks, and 3) Ca²⁺-stimulated maximal peak dp/dt and propranolol-induced minimal peak dp/dt were both greater at 18 weeks. Taken together these results demonstrate that cardiac contractile function was preserved at two time intervals despite the considerable duration of hypertension and the development of consequent LV hypertrophy.

This interpretation is consistent with the work of Pfeffer et al., who noted a preserved cardiac performance through most of the course in hypertension in SHR. Previous studies determining the baseline peak dp/dt indicated that this value was unaltered in isolated, artificially perfused hearts or in the in situ hearts from SHR.7 and Goldblatt hypertensive rats.5,8,9 while it was increased in anesthetized Page hypertensive rabbits10 and dogs.11 Our study dealing with conscious intact animals also indicates the uncompromised resting peak dp/dt in the DOCA-salt hypertensive model.

The increased resting peak dp/dt we observed in the 18-week DOCA-salt (compared with that in control rats) may be brought about largely by sympathoadrenergic support.2-5-6-8-9 as suggested by the greater decrease in peak dp/dt following β-adrenergic blockade with propranolol (see Table 3). Another factor would be an intrinsic component caused by increased total contractile units resulting from substantial LV hypertrophy in the presence of prolonged hypertension. The greater value of minimal peak dp/dt we observed following β-blockade in the 18-week DOCA-salt as compared to that in control rats might be a reflection of this possibility. Among other possible factors, reduced diastolic LV compliance did not appear to be important since no such abnormality was observed in the hearts of either SHR or Goldblatt rats.5

The ability of the heart to increase its contractility when stress is imposed is promoted mainly by endogenous sympathoadrenergic stimulation.1,6,8,9 This ability may be inferred by evaluating the peak dp/dt response to exogenous β-adrenergic stimulation with isoproterenol.2,5,6,8,9,11 In applying this concept and estimating contractile reserve as the difference between isoproterenol-activated maximal and resting peak dp/dt, we considered that, in the DOCA-salt rats, contractile reserve was unaltered at 9 weeks and was reduced at 18 weeks (see Table 2).

In addition, the difference between resting and propranolol-induced minimal peak dp/dt was greater at 18 weeks in the hypertensive rats (see Table 3). Taking this difference to be the β-adrenergic component of the resting contractile state, these findings suggest that the increased resting peak dp/dt we observed in the 18-week DOCA-salt rats was maintained by mobilizing a greater portion of total β-adrenergically mediated contractile capacity. In light of the lack of change in the Ca²⁺-induced increase in peak dp/dt these rats (see Table 2), the seemingly reduced contractile reserve implies that there may be alterations in the process of ventricular β-adrenergic receptor mediation proximal to Ca²⁺-triggered contraction, in accordance with the data on Goldblatt rats.8

Long-term augmentation of cardiac sympathetic drive and consequent decreases of β-adrenergic receptor concentrations may explain these events. Support for this speculation comes from the work of Woodcock et al.,24 who found decreases of β-adrenergic receptor density and decreases of isoproterenol-stimulated adenylate cyclase activity in ventricular membranes from rats with established DOCA-salt hypertension. The near-maximal response to isoproterenol we tested probably was related to receptor numbers. The observed greater response of peak dp/dt to propranolol also is consistent with the notion of diminished receptor density.

The equal responses of HR to isoproterenol and propranolol seen in the DOCA-salt rats and sham-treated rats indicate no alterations in β-adrenergic receptor mediated chronotropic responses in the DOCA-salt rats. Although this finding hardly reconciles with the altered peak dp/dt responses to these agents, it is possible that sinus and ventricular receptors possess different properties and therefore respond differently to isoproterenol, as was shown in the study of excited heart from Goldblatt rats.4

Resting and Maximal Coronary Flow

Regarding the coronary vasodilator effect of a 2 mg/kg/min dose of dipyridamole, we and Wangler et al.17 noted that doubling the dose produced no further coronary dilatation in either hypertensive or normotensive rats. Moreover, Wangler et al.17 offered compelling evidence that postischemic coronary reactive hyperemia no longer emerged during this dose of dipyridamole. These findings strongly suggest that the dose of dipyridamole we gave actually led to maximal or near-maximal coronary dilatation, which would validate this part of our study.

Our data revealed no alterations of resting and maximal CF in either the left or right ventricle and no alterations of LV and RV CF reserves in DOCA-salt hypertension (see Table 5). The similarity of the response pattern of the LV inner/outer flow ratio we observed in the DOCA-salt rats compared with that in sham-treated rats indicates an unaltered endocardial flow reserve. It should be noted that when maximal CF instead of change in flow was used as an indicator of CF reserve, the same conclusion was reached.14, 15, 18

These findings are essentially the same as those of Wangler et al. on young to old SHR with 14 to 28% increases in LV/body weight ratios.17 The LV CF reserve, assessed as maximal CF, was also shown to be normal in Goldblatt hypertensive rats with LV/body weight ratios of 50 to 58% increases.18 Similar observations were made in conscious dogs with Goldblatt and Page hypertension with 49% increases in LV/body weight ratios. Thus, all these studies as well
as ours involve mild to moderate degrees of hypertensive LV hypertrophy. The maintenance of normal CF reserve may be accounted for by the proposal of Wick-er et al.13 that a balance between increases in arterial pressure and LV mass may be appropriate in these hypertensive left ventricles, assuming that CF becomes pressure dependent at maximal coronary dilation. In support of this proposal several studies15-22 of animals with more marked LV hypertrophy resulting from ascending aortic constriction, in which diastolic coronary perfusion pressure was not as increased as in systemic hypertension,23 provided evidence for a decreased CF reserve, particularly of the endocardial lay-ers. Furthermore, the same evidence was obtained in dogs with severe RV hypertrophy caused by pulmo-nary artery stenosis that was not accompanied by any increase in coronary perfusion pressure.24

Our findings of no change in minimal total LV CVR and the increase in minimal normalized LV CVR in the DOCA-salt rats (see Table 5) are in keeping with earlier reports on other forms of hypertension.14-18 The use of the minimal total CVR as an index of the cross-sectional area of the coronary vascular bed19, 20 suggests the lack of increases in the functional cross-sectional area proportionate with increases in LV mass. The use of the minimal normalized CVR as an index of coronary vascular hypertrophy suggests the occurrence of LV coronary structural alterations.14, 21 Such architectural and structural factors are also deduced from data in a report on the lack of abnormalities in metabolic coronary regulation and adenosine release in the hearts of renal hypertensive dogs.16 The remarkable finding of the increase in both minimal total and minimal normalized RV CVR associated with no increase in RV mass in our DOCA-salt rats suggests that more anatomical changes occur in the right ventricle than in the LV coronary bed. This difference may be ascribed to chronic exposure of the RV vasculature to elevated coronary perfusion pressure in the absence of hypertrophic stimulus.17

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