SUMMARY It has been suggested that central nervous system (CNS) neuroexcitation plays an important role in digitalsis-induced cardiac arrhythmias. To elucidate further the role of the CNS in digitalis-induced arrhythmias, the inotropic and toxic effects of a highly polar semisynthetic cardiac glycoside, 3β-D-(4-amino-4,6-dideoxy-β-D-galactopyranosyl)-digitoxigenin (ASI-222) were compared to those of digoxin and correlated with plasma and cerebrospinal fluid (CSF) concentrations of each drug. Thirteen dogs anesthetized with sodium pentobarbital were given repeated intravenous doses of digoxin or ASI-222. Ventricular tachycardia was elicited at a mean dose of digoxin of 0.12 mg/kg, compared with 0.09 mg/kg for ASI-222 (not significant). Terminal ventricular fibillation occurred after 0.18 mg/kg of digoxin, a value significantly larger than the ASI-222 dose (0.14 mg/kg, \( P < 0.05 \)) required to produce lethal arrhythmias. Digoxin produced a 21% increase in LV dP/dt at a plasma digoxin concentration of 20.0 ± 2 ng/ml (mean ± SEM) 30 minutes after 0.05 mg/kg; the CSF digoxin concentration at this time averaged 0.7 ± 0.1 ng/ml. At death, the plasma digoxin concentration was 88 ± 16 ng/ml and CSF digoxin concentration was 5.7 ± 1.6 ng/ml. ASI-222 produced a similar 25% increase in LV dP/dt 30 minutes after administration of 0.05 mg/kg, with a plasma concentration of 18 ± 2 ng/ml as determined by a newly developed radioimmunoassay. The plasma ASI-222 concentration at death, 95 ± 18 ng/ml, was similar to that of digoxin. However, CSF samples at 30 minutes and at death showed no detectable levels of ASI-222. Thus, despite similar inotropic and toxic responses and similar plasma drug concentrations compared to digoxin, ASI-222 was demonstrated to have limited if any access to the CNS as judged by CSF concentrations. These findings suggest that direct CNS stimulation does not play a primary part in the genesis of digitalis-induced cardiac arrhythmias in this experimental model, or that CNS effects are mediated by an area or areas lacking an effective blood-brain barrier.

THERAPEUTIC use of cardiac glycosides is complicated by frequent signs and symptoms of cardiac and extracardiac toxicity, and the narrow margin between therapeutic inotropic effect and serious cardiac arrhythmias is well known. Recent experimental evidence suggests that digitalis-induced central nervous system (CNS) neuroexcitation contributes to cardiac rhythm disturbances. Ventricular arrhythmias have been temporally related to enhanced cardiac sympathetic neural activity or to...
increased dispersion of sympathetic activity in different cardiac sympathetic nerve fibers. Alteration of sympathetic neural activity by surgical sympathectomy or high spinal cord transection increases the dose of digoxin required to produce fatal arrhythmias in vagotomized cats. Whether or not these effects result from central or peripheral neural stimulation, however, is the subject of continuing debate.

To elucidate further the role of CNS stimulation in digitalis-induced arrhythmias, we undertook the present studies with a semisynthetic aminosugar cardiac glycoside derivative, 3-β-O-(4 amino-4,6-dideoxy-β-D-galactopyranosyl) digitoxigenin (ASI-222), the structure of which is shown in Figure 1. This agent has been reported by Caldwell and co-workers to have pharmacological properties typical of cardiovascular glycosides, including the ability to inhibit Na⁺-K⁺ ATPase, to induce positive inotropic responses in isolated atrial strips and in intact animals, and to enhance Purkinje fiber automaticity. We reasoned that such a cardiac glycoside derivative, being relatively polar, would not readily penetrate the blood-brain barrier and would, therefore, have limited access to the CNS. If direct CNS stimulation plays an important part in the genesis of digitalis-induced arrhythmias, then a derivative such as ASI-222 might be expected to have an enhanced toxic-to-therapeutic dose ratio. In the studies reported here, the inotropic and arrhythmogenic effects of ASI-222 were compared to those of digoxin. A sensitive radioimmunoassay for ASI-222 was developed, and plasma and cerebrospinal fluid (CSF) concentrations of ASI-222 and digoxin were correlated with the inotropic and arrhythmogenic effects of these drugs. This assay was used further to determine the pharmacokinetics of ASI-222 in the dog.

**Methods**

**Radioimmunoassay**

Digoxin concentrations in plasma and CSF were measured by radioimmunoassay as previously described. A radioimmunoassay was developed for ASI-222. Selected antiserum from a sheep immunized with a digoxin-albumin conjugate was found to bind [3H]-digitoxin with high affinity. [3H]-Digitoxin, 0.5 ng (New England Nuclear; specific activity, 10.9 Ci/mmol), and varying concentrations of ASI-222 were incubated with an appropriate amount of antiserum for 20 minutes in 1.0 ml of a 1:1 mixture of phosphate-buffered saline (0.15 M NaCl, 0.01 M Na₂HPO₄, adjusted to pH 7.4 with H₃PO₄) (PBS) and canine plasma. Dextran-coated charcoal was then added to remove free glycoside components, and the mixture was centrifuged for 20 minutes at 5000 g. The supernatant phase was decanted into scintillation counting medium and counted in a liquid scintillation spectrometer. Tritium internal standards were used for quench correction. The percent of antibody-bound [3H]-digitoxin was plotted as a function of known concentrations of ASI-222 to construct a standard curve, from which unknown values were estimated. Plasma concentrations of ASI-222 or digoxin were determined with dilution of plasma, when necessary, to place each unknown sample on the steep portion of the standard curve. ASI-222 and digoxin concentrations in CSF were determined using 0.5 ml CSF in place of PBS. All samples were determined in duplicate.

Specificity of the ASI-222 assay was documented by determining the displacement of [3H]-digitoxin from antibody-binding sites by endogenous steroid compounds including cholesterol, cortisol, dehydroepiandrosterone, 17β-estradiol, testosterone, and progesterone in concentrations substantially greater than those known to occur physiologically. Precision was assessed by determination of agreement on duplicate samples run in the course of the study.

To permit further interpretation of data relating to CSF concentration, the pKa of ASI-222 was determined by titration of a 2 mM solution in deionized, glass-distilled water flushed with nitrogen to exclude CO₂. The pKa, corrected for solvent effects, was 7.14. Plasma protein binding studies of ASI-222 concentrations from 2 to 20 ng/ml were performed by equilibrium dialysis as previously described. ASI-222 was allowed to equilibrate between canine plasma and PBS for 24 hours. Control experiments showed that full equilibrium was reached by this time irrespective of whether ASI-222 was added to the PBS or to the plasma side of the membrane. Concentrations on both PBS and plasma sides of the dialysis membrane were then measured by radioimmunoassay. Plasma protein binding averaged 70 ± 1% (mean ± SEM) with a range of 64 to 76% for concentrations from 2 to 20 ng/ml.

**Figure 1** Structure of 3-β-O-(4 amino-4,6-dideoxy-β-D-galactopyranosyl) digitoxigenin (ASI-222).
Pharmacokinetics of ASI-222

To establish the pharmacokinetics of ASI-222 in the dog, three male dogs (20 ± 2 kg) were studied. On the day prior to study, the dogs were anesthetized with intravenous sodium pentobarbital (30 mg/kg). An internal jugular vein was exposed and cannulated with a polyethylene catheter which was kept filled with 0.9% normal saline containing heparin (200 U/50 ml saline). The following day, when the dogs had fully recovered from this procedure, ASI-222 was injected into a peripheral vein in a dose of 0.07 mg/kg. Venous blood samples were drawn via the previously positioned catheter at the completion of ASI-222 administration and after 5, 15, 30, 45, and 60 minutes and 1.5, 2, 3, 4, 6, 8, 12, 24, 32, and 48 hours. Plasma was immediately separated and stored at −20°C for subsequent radioimmunoassay.

Plasma ASI-222 pharmacokinetics following intravenous injection were analyzed by computer using weighted nonlinear least squares regression analysis.21 The residual error for each data point, prior to squaring, was weighted by a factor equal to the reciprocal of the square root of that concentration. The data for each dog were fitted to functions of the form:

\[ C = Ae^{-at} + Be^{-bt} \]

\[ C = Ae^{-at} + Pe^{-et} + Be^{-ft} \]

where C is the plasma concentration at time t after administration, A, P, and B are hybrid coefficients having units of concentration, and \( \alpha, \pi, \text{and} \beta \) are hybrid exponents having units of reciprocal time. The triexponential function was found to fit the data better than the biexponential function. Computer-generated functions were used to calculate the following parameters:20 apparent distribution half-life (\( t_{\alpha} \)), intermediate half life (\( t_{\pi} \)), apparent elimination half life (\( t_{\beta} \)), volume of central compartment (\( V_i \)), total apparent volume of distribution using the area method (\( V_d \)), and total clearance.

Assessment of Inotropic and Toxic Effects

Male dogs, weighing 20 ± 2 kg, were anesthetized with intravenous sodium pentobarbital, 30 mg/kg, intubated, and ventilated with 95% oxygen-5% CO\(_2\) using a Harvard positive pressure respirator. Respiratory rate and tidal volume were adjusted to maintain normal blood gas tensions and pH, and these values were monitored. A standard lead II electrocardiogram was continuously recorded. Both femoral arteries and veins were exposed. A percutaneous endocardial pacing catheter was placed in the right ventricle via the femoral vein under fluoroscopic control. Heart rate was maintained at 150 beats/min with a Medtronic 5840 pacemaker. Left ventricular pressure was recorded by a high fidelity micromanometer-tipped catheter passed retrograde from the femoral artery, and the first derivative of LV pressure, dP/dt, recorded with the use of an RC circuit with a time constant of 0.5 msec and an output linear to 75 Hz (5% error at 125 Hz, 10% error at 160 Hz), connected in turn to a DC amplifier channel.21 Arterial pressure was monitored via a catheter passed from the femoral artery to the central aorta.

To permit estimation of the amount of drug reaching the extracellular space of the CNS, the cisternum magnum was punctured with an 18-gauge spinal needle, and 2-ml samples of CSF collected. After initial control hemodynamic recordings, 0.05 mg/kg of digoxin (Lanoxin, Burroughs-Wellcome) or ASI-222 (Ash-Stevens Institute, Detroit) was administered intravenously over a period of 2 minutes. Thirty minutes after the injection, the electrocardiogram, left ventricular maximum dP/dt (LV dP/dt), and arterial pressure were recorded and arterial blood and CSF sampled. A second injection of digoxin (0.05 mg/kg) or ASI-222 (0.05 mg/kg) was then given, and repeat recordings and samples were taken again after 30 minutes. This process was repeated until a terminal arrhythmia, ventricular fibrillation in all cases, resulted. Eight dogs received ASI-222 and five received digoxin. Dogs in which the cisternum magnum puncture was traumatic, as indicated by macroscopic evidence of erythrocytes in the CSF, were excluded from the study.

Statistical evaluation was by Student’s t-test (unpaired), and differences in means were considered significant when \( P \) values were less than 0.05.

Results

Radioimmunoassay

Displacement of \(^3\)H-digitoxin from antibody binding sites by ASI-222 is illustrated in Figure 2. As shown, ASI-222 concentrations as low as 0.1 ng/ml can be reliably measured. Figure 2 also summarizes the results of specificity studies, which demonstrated the absence of interference by the steroid compounds cholesterol, cortisol, dehydroepiandrosterone, 17-βestradiol, testosterone, and progesterone, in concentrations in large excess above those occurring physiologically. The mean difference between duplicate values obtained from all samples measured in this study was 5.5 ± 4.1% (SD).

Pharmacokinetics

Mean plasma ASI-222 concentrations following intravenous administration to three conscious dogs are plotted in Figure 3 as a function of time. Pharmacokinetic variables calculated from computer-fitted functions are summarized in Table 1. The plasma level of ASI-222 fell rapidly at first, with a mean distribution phase half-life (\( t_{\alpha} \)) of 0.9 minute. The mean elimination phase half-life (\( t_{\beta} \)) was 24.3 hours. The mean volume of the central compartment (\( V_i \)) was 0.18 liter/kg, and the mean ap-
parent volume of distribution measured by the area method ($V_d$) was 26.9 liters/kg. Mean total ASI-222 clearance was 12.8 ml/min per kg. As noted previously, plasma protein binding as determined by equilibrium dialysis was extensive, averaging 70% over the range from 2 to 20 ng/ml.

**Inotropic Responses**

The inotropic responses to digoxin and ASI-222 are summarized in Figure 4. Thirty minutes after the initial 0.05 mg/kg dose of digoxin, there was a 21% mean increase in peak LV dP/dt over control recordings. This was not significantly different from the 25% increase in LV dP/dt recorded following initial ASI-222 administration. One of the eight dogs receiving ASI-222 developed ventricular premature beats following 0.05 mg/kg, and is excluded from the inotropy data. All other dogs remained in normal sinus rhythm following the initial injection.

With the second dose of digoxin, there was a further increase in LV dP/dt; all dogs receiving digoxin remained in normal sinus rhythm after the second 0.05 mg/kg dose. Although a similar increase in LV dP/dt also was recorded following the second injection of ASI-222, four of the seven dogs receiving ASI-222 developed ventricular tachycardia at this dose level, preventing valid comparison of LV dP/dt data. The data shown in Figure 4 for ASI-222 after 0.10 mg/kg are for the three dogs that did not develop arrhythmias at this dose level.

**Toxic and Lethal Doses**

Sustained ventricular tachycardia was induced after a mean dose of 0.09 ± 0.02 (mean ± SEM) mg/kg of ASI-222. This was not significantly different from the toxic dose found for digoxin, 0.12 ± 0.01 mg/kg. With continued administration of ASI-222 or digoxin, all dogs died in ventricular fibrillation. However, a significantly greater dose of digoxin, 0.18 ± 0.01 mg/kg, was required to produce

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**Table 1: Plasma Pharmacokinetics of ASI-222**

<table>
<thead>
<tr>
<th>Dog</th>
<th>$t_{1/2}$ (min)</th>
<th>$t_{1/2}$ (hr)</th>
<th>$t_{1/2}$ (hr)</th>
<th>$V_a$ (liters/kg)</th>
<th>$V_d$ (liters/kg)</th>
<th>Total clearance (ml/min per kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>0.11</td>
<td>16.5</td>
<td>0.16</td>
<td>17.8</td>
<td>12.5</td>
</tr>
<tr>
<td>2</td>
<td>1.37</td>
<td>0.22</td>
<td>32.2</td>
<td>0.16</td>
<td>34.7</td>
<td>12.4</td>
</tr>
<tr>
<td>3</td>
<td>1.24</td>
<td>0.34</td>
<td>24.1</td>
<td>0.23</td>
<td>22.2</td>
<td>13.5</td>
</tr>
<tr>
<td>Mean</td>
<td>0.88</td>
<td>0.22</td>
<td>24.3</td>
<td>0.18</td>
<td>26.9</td>
<td>12.8</td>
</tr>
</tbody>
</table>

$V_a$: volume of central compartment; $V_d$: total apparent volume of distribution.

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*Abbreviations: $t_{1/2}$ = apparent distribution half-life; $t_{1/2}$ = intermediate pi half-life; $t_{1/2}$ = apparent elimination half-life; $V_a$ = volume of central compartment; $V_d$ = total apparent volume of distribution.
INOTROPY AND TOXICITY OF A POLAR CARDIAC GLYCOSIDE/Mudge et al.

the terminal arrhythmia than in the case of ASI-222, 0.14 ± 0.01 mg/kg ($P < 0.05$). Thus, despite similar positive inotropic effects, ASI-222 produced ventricular fibrillation at significantly lower doses than digoxin.

**Plasma and CSF Digoxin Concentrations**

Plasma and CSF digoxin concentrations were determined 30 minutes after each digoxin dose and at the time of death. These data are summarized in Figure 5. With the initial dose, coincident with a 21% mean increase in $dP/dt$, the plasma digoxin concentration was 20 ± 2.0 ng/ml, and the concomitant mean CSF concentration was 0.7 ± 0.1 ng/ml. With further digoxin doses, both plasma and CSF concentrations rose, and at the time of ventricular fibrillation, the mean plasma digoxin concentration was 88 ± 16 ng/ml, with a simultaneous mean CSF concentration of 5.7 ± 1.6 ng/ml. The CSF-to-plasma concentration ratio following the initial digoxin dose was 0.04, and at death was 0.06. These values are similar to value of 0.05 found in previous investigations with digoxin.$^{16}$

**Plasma and CSF ASI-222 Concentrations**

The results of plasma and CSF ASI-222 concentration determinations are summarized in Figure 6. Thirty minutes after the initial 0.05 mg/kg dose, associated with a 25% increase in LV $dP/dt$, the plasma ASI-222 concentration was 18 ± 2.0 ng/ml. This value was not significantly different from the digoxin concentration found at the same time after a 0.05 mg/kg dose of digoxin. However, there was no detectable ASI-222 in the CSF. With additional doses, the plasma ASI-222 concentration rose progressively, and at death was 95 ± 18 ng/ml, similar to the plasma digoxin concentration at death. In the CSF, ASI-222 concentrations continued to be below levels detectable by radioimmunoassay in all dogs studied. Thus, despite similar plasma total concentrations, similar inotropic effects, and similar toxic arrhythmic manifestations when compared to digoxin, ASI-222 did not penetrate into the CSF in detectable amounts.

**Discussion**

There is substantial evidence suggesting that the nervous system participates in the toxic arrhythmogenic effects of cardiac glycosides. Studies by Erlij and Mendez$^8$ and Boyajy and Nash$^9$ have shown that surgical sympathectomy, reserpine, or β-adrenergic blockade with nethalide changed the terminal digitalis-induced arrhythmic event from ventricular fibrillation to ventricular stand-still. Such pharmacological or surgical interventions also increased the dose of glycoside required to produce terminal arrhythmias. Gillis and co-workers have demonstrated enhanced sympathetic, vagal, and phrenic neural activity coincident with digitalis-toxic cardiac rhythm disturbances in vagotomized cats. They found enhanced pre- and postganglionic sympathetic neural activity in response to ouabain$^4$ and digoxin$^5$ with maximal increases in activity just

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**Figure 4** Positive inotropic responses to ASI-222 and digoxin in the intact dog. Mean percent changes in left ventricular maximum $dP/dt$ after total doses of 0.05 and 0.10 mg/kg of each glycoside are shown.

**Figure 5** Plasma and CSF digoxin concentrations (ng/ml) 30 minutes after serial 0.05 mg/kg injection until death. The left vertical scale indicates plasma concentrations; the CSF scale is at the right.

**Figure 6** Plasma and CSF ASI-222 concentrations (ng/ml) 30 minutes after serial 0.05 mg/kg injection until death. The left vertical scale indicates plasma concentrations; the CSF scale is at the right.
primary amino group renders this semisynthetic cardiac glycoside relatively polar at physiologic pH, thus potentially limiting blood-brain barrier permeability. Substantial binding of ASI-222 by plasma proteins would be expected further to limit access to portions of the CNS with a normal blood-brain barrier.

To correlate inotropy and toxicity data with CNS drug penetration, CSF and plasma concentrations of ASI-222 following intravenous administration were measured and compared to data for digoxin. This required the development of a sensitive assay for ASI-222. The radioimmunoassay for ASI-222 reported here permits simple and rapid determination of plasma and CSF ASI-222 concentrations. This approach is similar to radioimmunoassay techniques previously developed for other cardiac glycosides and avoids the necessity of extraction procedures. Sensitivity, precision, and specificity data for the ASI-222 assay are comparable to values obtained in the previous studies cited.

The results of the present study show that a semisynthetic aminosugar cardiac glycoside, ASI-222, when compared to digoxin in the dosage schedule used, has a similar positive inotropic effect, but requires significantly lower doses to produce lethal toxicity. Penetration of the blood-brain barrier by ASI-222 could not be detected. The lack of penetration of the blood-brain barrier by ASI-222 cannot be explained by rapid metabolism or excretion. The pharmacokinetics of plasma ASI-222 follow a pattern similar to that observed with digoxin. The mean elimination phase half-life (t½β) of 24.3 hours for ASI-222 is similar to earlier estimates of t½β for digoxin (in dogs) of 26 to 27 hours.

It should be noted that there is a discrepancy in ASI-222 plasma concentrations between the pharmacokinetic studies and protocols designed to determine inotropic and arrhythmogenic effects. In the former, 0.07 mg of ASI-222 produced a mean plasma concentration of 7.5 ng/ml 30 minutes after injection, whereas, in the latter studies, 0.05 mg/kg produced a mean plasma concentration of 18 ng/ml after the same time period. The reasons for this difference are uncertain, but may be related to hemodynamic differences between the conscious dogs used in the pharmacokinetic studies and dogs under pentobarbital general anesthesia.

Caldwell and Nash have reported the therapeutic index for ASI-222, defined as the ratio of lethal or arrhythmogenic dose to inotropic dose, to be more than twice that of ouabain in dogs. They also reported a significantly greater increase in maximal contractile force of isolated rabbit atria with ASI-222 when compared to ouabain. In these studies, terminal arrhythmias were produced in dogs after a cumulative intravenous dose of 0.24 mg/kg of ASI-222. This is nearly twice the mean lethal dose observed in the present studies, which used a similar anesthetic protocol. The discrepancy may be due to the different rate of ASI-222 administration (0.016 mg/kg every 20 minutes as compared to 0.05 mg/kg every 30 minutes in our experiments). This
inference is supported by comparison of our results with results of other studies using dosage schedules of ASI-222 and digoxin comparable to our own. In the latter studies, Caldwell and co-workers found ASI-222 to have inotropic and arrhythmogenic effects compared to digoxin that are consistent with our own observations.

Since drugs with direct CNS stimulatory effects in general appear in the extracellular fluid of the CNS and hence in the CSF, the absence of detectable ASI-222 in the CSF suggests that direct CNS stimulation does not play a primary part in the genesis of digitalis-induced cardiac arrhythmias. This tentative conclusion must be viewed with caution, however, since discrete areas of the brain are known to be devoid of an effective blood-brain barrier. The area postrema of the medulla, posterior lobe of the pituitary, pineal body, choroid plexus, and wall of the optic recess are permeable to trypan blue. The area postrema has been identified by Wang and associates as the locus for the central emetic action of digitalis. Recently reported high ouabain concentrations in the pituitary and choroid plexus following systemic administration. The vascular pattern in these regions is devoid of an effective blood-brain barrier and is markedly different from that of the remaining central nervous system, having numerous vascular sinusoids with no perivascular glial membrane. We cannot exclude the possibility that ASI-222 may have a direct stimulatory effect in these neuroanatomic loci.

The radioimmunoassay for ASI-222 as used in these studies has a sensitivity of 0.1 ng/ml and thus could have failed to detect smaller CSF concentrations. Such undetectable concentrations of ASI-222 could conceivably be all that is required for direct CNS stimulation. However, the CSF digoxin concentrations reported here at the time of death are at least 50 times greater than the maximum possible ASI-222 concentrations, despite similar plasma concentrations and cardiac inotropic and arrhythmogenic effects of these two drugs.

We conclude from these studies that the polar semisynthetic cardiac glycoside ASI-222 has limited access to the CNS. Nonetheless, it has similar toxic as well as inotropic potencies compared to digoxin, a drug that readily penetrates the blood-brain barrier. Although our findings do not exclude central neural effects at loci without an effective blood-brain barrier, these data do not provide support for a primary role of direct CNS stimulation in the genesis of digitalis-toxic cardiac arrhythmias.

References

Direct Evidence that the Greater Contractility of Resistance Vessels in Spontaneously Hypertensive Rats is Associated with a Narrowed Lumen, a Thickened Media, and an Increased Number of Smooth Muscle Cell Layers

MICHAEL J. MULVANY, POU1 KUNG HANSEN, AND CHRISTIAN AALKJØR

SUMMARY The mechanical and morphological properties of segments of certain precisely defined resistance vessels (~150 μm lumen diameter) in the mesenteric bed of spontaneously hypertensive (SHR) and normotensive (WKY) rats have been compared in vitro under carefully controlled conditions and also after fixation. At a given transmural pressure, the relaxed SHR vessels (compared with the WKY vessels) would have had a 16% smaller lumen diameter ($P < 0.01$) and a 49% thicker media ($P < 0.005$), so that the media volume per unit segment length was 31% greater ($P < 0.05$). The smooth muscle cells were arranged circumferentially in about four layers in the SHR vessels and in about three layers in the WKY vessels. The SHR active wall tension in response to potassium was 53% greater ($P < 0.02$) and to norepinephrine was 50% greater ($P < 0.01$) than for WKY. However, the ED$_{50}$ values for the norepinephrine dose-response curves were similar (~5 μM). Activation with potassium plus norepinephrine gave greater responses in both vessel types, than with either agent alone, but the SHR responses were on average only 19% greater than the WKY ($P < 0.10$). However, under these conditions, the SHR vessels would have been able to contract against 45% greater transmural pressures ($P < 0.001$) because of their smaller lumen. On maximal activation, the mean force developed by each cell (~3.85 mN) was the same in both vessel types, even though on average ($P = 0.10$) the SHR cells had a 21% greater cross-sectional area. The results support the Folkow hypothesis that in genetic hypertension the increased peripheral resistance is associated with structural changes in the resistance vessels.

HEMODYNAMIC studies on the spontaneously hypertensive rat (SHR)—widely used as a model for human essential hypertension—show that the total peripheral resistance is abnormally high both under in vivo conditions and when experimentally relaxed. Although some evidence suggests that this high resistance is due to an abnormally low number of resistance vessels, it generally is concluded that the high resistance is due mainly to abnormally small lumen diameters of the resistance vessels. However, the only direct evidence for the latter hypothesis has been provided by the detailed study of Ichijima, who demonstrated that the lumen diameters of resistance vessels in anesthetized SHR are smaller than those found in Wistar-Kyoto (WKY) controls.

This lack of evidence for structural changes contrasts with the large number of findings concerning
Inotropic and toxic effects of a polar cardiac glycoside derivative in the dog.
G H Mudge, Jr, B L Lloyd, D J Greenblatt and T W Smith

Circ Res. 1978;43:847-854
doi: 10.1161/01.RES.43.6.847

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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