HUMAN essential hypertension is associated with an elevated blood pressure but a normal cardiac output. The total peripheral resistance is therefore elevated. The cause of this elevation is not clear but a genetic factor seems to be involved. As a means to investigate genetic hypertension in detail, a strain of spontaneously hypertensive rats (SHR) has been developed by Okamoto and his colleagues from a colony of Wistar-Kyoto rats (WKY). These SHR reach a stage of established hypertension by the age of 5 months. At this time their systolic blood pressure is about 50% higher than that of their WKY controls although, as in human essential hypertension, their cardiac output is normal.

The vascular bed of these rats contains vessels with diameters ranging from 3 mm in the aorta to about 7 μm in the capillaries. Although all these vessels must contribute to the resistance of the vascular bed to some extent, it is general the smaller arterial resistance vessels which present the greatest resistance, and which are most involved in regulating blood flow and capillary pressure. Perfusion studies on isolated vessels have been able to contract against 34% greater pressures than the WKY vessels (P < 0.001). Optical measurements of these vessels showed a 23% greater wall thickness in the SHR vessels (P < 0.02). There were no significant differences in the calculated active wall stresses of the SHR and WKY vessels; this suggests that the greater contractility found in the SHR vessels may be due to their having a greater smooth muscle cell content. These vessel measurements have been examined as well as the rats’ blood pressures and heart to body weight ratios. The comparison points to the possibility that the disturbance to the cardiovascular regulatory system which results in hypertension produces similar cellular responses in both the myocardium and the peripheral vasculature.

SUMMARY The small arteries play an important functional role in establishing the increased peripheral resistance found in essential hypertension. This paper concerns the direct measurement of the intrinsic mechanical and contractile properties of two categories of small arterial resistance vessels in the mesenteric bed of 5-month-old normotensive Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). The vessels had mean internal diameters of 246 μm and 153 μm when relaxed at 100 mm Hg effective transmural pressure. Segments (1 mm) were mounted in such a way that internal circumference could be controlled and the circumferential wall tension (T) measured. After mounting, each vessel was maximally activated (by K+ depolarization at 37°C in the presence of 5 mM Ca++) at an internal circumference for which ΔT was approximately maximal, where ΔT = T(active) - T(relaxed). From the average values of ΔT measured we have estimated (on the basis of Laplace’s equation) that the SHR vessel would have been able to contract against 34% greater pressures than the WKY vessels (P < 0.001). Optical measurements of the dimensions of these vessels showed a 23% greater wall thickness in the SHR vessels (P < 0.02). There were no significant differences in the calculated active wall stresses of the SHR and WKY vessels; this suggests that the greater contractility found in the SHR vessels may be due to their having a greater smooth muscle cell content. These vessel measurements have been examined as well as the rats’ blood pressures and heart to body weight ratios. The comparison points to the possibility that the disturbance to the cardiovascular regulatory system which results in hypertension produces similar cellular responses in both the myocardium and the peripheral vasculature.

Although there is evidence to suggest that the various portions of the vasculature react differently, the work with isolated vessels has been largely confined to the aorta and various conduit arteries and smaller arteries having internal diameters greater than 300 μm. Technical difficulties have hitherto prevented direct data being obtained from smaller vessels. It is clear however that such data is of importance in understanding the action of the vasculature and we have therefore developed a method first proposed by Bevan and Osher to make direct mechanical measurements on intact segments from small vessels. With this method we have investigated vessels from SHR and WKY having diameters in the range 75–300 μm. Our studies have been confined to determining the intrinsic mechanical and contractile properties of these vessels. We have therefore limited our experiments to the examination of vessels either when they were fully activated or when they were fully relaxed.

Methods

ANIMALS

The SHR and their WKY controls were bred in our own colony from a pair provided by the National Institutes of Health. Systolic blood pressures were measured by the tail-cuff method. Experiments were performed when the rats were about 5 months old.

DISSECTION

The arterial resistance vessels used were the first and second branches of mesenteric arcades. The second branch resistance vessels are those that directly enter the
aminetetraacetic acid (EDTA), 0.026; glucose, 5.5; and
SOLUTIONS

4.7; KH₂PO₄, 1.18; MgSO₄, 1.17; CaCl₂, 1.6; ethylenediaminetetraacetic acid (EDTA), 0.026; glucose, 5.5; and

intestinal wall; they stem from first branches (Fig. 1a). One vessel segment was taken from each rat and threaded onto two parallel tungsten wires; the wires in turn were attached to two specimen supports (Fig. 1b and c). During this process, which took about 1 hour, the vessel was kept cool (5-15°C) in Ringer’s solution. Vessel segments were about 0.7 mm long (but 1.5 mm long in some experiments in which larger specimen supports were used). After mounting, the vessels were equilibrated at an internal circumference for which the wall tension (see below) was about 0.2 mN/mm.

APPARATUS

The myograph used is shown in Figure 2. The specimen supports were mounted, respectively, on a tension transducer and a displacement device. The latter measured the circumference to be controlled. A heat exchanger kept the supports were mounted, respectively, on a tension transducer (DSC 6, Kistler-Morse, lowest resonant frequency with support mounted-400 Hz) and a piezoelectric vibrator (PZ40, Burleigh; frequency range, 0-2,000 Hz). The latter was mounted on a micrometer translator. An eddy-current displacement transducer (KD 2300.5 SU, Kaman Sciences) monitored movement of R. The chamber was heated by thermostatically controlled water circulating through the myograph block. Solutions entered and left the chamber as indicated by the arrows. The myograph was constructed of Teflon-coated brass and was mounted on the stage of a microscope (Universal, Zeiss). Transmission illumination was used, the light from the condenser (Wl7, Zeiss) entering the chamber through a small glass window inserted beneath the supports. The working distance of the objective (40x, water immersion, NA = 0.75, Zeiss) and condenser were 1.2 mm and 7 mm, respectively, and sufficient to allow free circulation of the solution around the preparation.

VEssel DIMENSIONS

The following dimensions were measured with the vessel set to internal circumference, L₁ (see below): mean wall thickness, wₗ (average of 5-10 measurements); mean wire thickness, d (average of six measurements); mean distance between the inner edges of the wires, f₁ (average of three measurements); mean vessel segment length, l₂ (average of two measurements). As the vessel wall was found to be flat between the wires the internal circumference, L₁, was calculated from:

\[ L₁ = (\pi + 2)d + 2f₁. \]

Dimensions were measured with the vessel in Ringer’s solution after it had been activated at least twice. The internal circumference when the vessel was stretched or released from L₁ was determined from the displacement transducer output. The segment length was not found to change with stretch or release or following activation.

Vessels were equilibrated in a modified Ringer’s solution²⁸ containing (mm): NaCl, 119; NaHCO₃, 14.9; KCl, 4.7; KH₂PO₄, 1.18; MgSO₄, 1.17; CaCl₂, 1.6; ethylenediaminetetraacetic acid (EDTA), 0.026; glucose, 5.5; and

activated or relaxed in a K⁺ solution in which there was an equimolar substitution of KCl for NaCl and a substitution of 5 mM CaCl₂ (activating solution) or 1 mM ethylene glycol-bis[β-aminohydroxy ether]-N,N′-tetraacetic acid (EGTA) (relaxing solution) for the 1.6 mM CaCl₂. Graded activation was obtained by varying the CaCl₂ concentration in the K⁺ solution. All solutions were adjusted to pH 7.4, oxygenated externally with 95% O₂-5% CO₂ and circulated at 8 ml/min at 37°C. EDTA and EGTA were obtained from Sigma.

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From the measurements of both of these dimensions and of the force, F, exerted by vessels on the tension transducer, the following parameters have been derived:

1. Wall tension, T: Circumferential wall force per unit length given by:
   \[ T = \frac{F}{2\pi r} \]

2. Active wall tension, \( \Delta T \): Change in wall tension upon isometric activation given by:
   \[ \Delta T = T_{\text{active}} - T_{\text{relaxed}} \]
   where \( T_{\text{active}} \) and \( T_{\text{relaxed}} \) are the wall tensions in activating and relaxing solutions, respectively.

3. Active wall stress, \( \Delta \sigma \): Active wall tension per unit wall thickness given by:
   \[ \Delta \sigma = \frac{\Delta T}{w} \]
   where \( w \) is the wall thickness.

Under physiological conditions the in situ vessels must have been under a transmural pressure and have had an approximately circular cross section. On this basis the following “effective” parameters were calculated:

1. Effective lumen diameter, l: The calculated effective diameter corresponding to the determined internal circumference, \( L \), given by:
   \[ l = \frac{L}{\pi} \]

2. Effective transmural pressure, \( p \): Effective pressure calculated (on the basis that the vessel wall was sufficiently thin for Laplace’s equation to apply, and for it to be unaffected by the curvature imposed by the wires) from the equation:
   \[ p = \frac{2\pi T}{L} \]
   where \( L \) is the internal circumference corresponding to wall tension \( T \). In other words \( p \) is an estimate of the transmural pressure which would have been required to maintain the in situ vessel at the same internal circumference and wall tension under the same activation or relaxation conditions.

3. Effective active pressure, \( \Delta p \): Change in effective transmural pressure upon isometric activation given by:
   \[ \Delta p = p_{\text{active}} - p_{\text{relaxed}} \]
   where \( p_{\text{active}} \) and \( p_{\text{relaxed}} \) are the effective transmural pressures in activating and relaxing solutions, respectively.

4. Contractility: This term is here used synonymously with effective active pressure, indicating the ability of a vessel to contract against a given pressure.

Vessels were immersed in relaxing solution and stretched in steps of about 10 \( \mu \)m until the wall tension was about 1 mN/mm. The vessels were then released in similar steps until the tension was about zero. Vessels were held at each length for 1 minute and the wall tension immediately before the next step was taken as the wall tension at the internal circumference concerned. The points obtained could be fitted by an exponential curve.25

Vessel dimensions were normalized by using the resting wall tension-internal circumference curve determined as described above. \( L_{100} \) was defined as the internal circumference corresponding to the point on the fitted exponential curve for which the effective transmural pressure was 100 mm Hg. Thus \( L_{100} = L_100/\pi \) is an estimate of the lumen diameter the vessel would have had in situ when relaxed and under a transmural pressure of 100 mm Hg. For reasons given below the experiments described in this paper were performed at an internal circumference \( L_1 = 0.8 L_{100} \), except where stated otherwise.

Vessels were fixed at \( L_1 \). Before fixation vessels were equilibrated in the chamber in relaxing solution for at least 15 minutes. The chamber was then drained and refilled with prefixative (2.5% glutaraldehyde, 7% sucrose in 75 mm cacodylate, 37°C) and left overnight at room temperature. The solution was then changed to cacodylate buffer and the wires were carefully removed from the vessel. The vessel was then postfixed in 1% OsO\(_4\), blockstained with uranyl acetate, and embedded in Epon.28 Thick sections (0.5 \( \mu \)m) were cut from the block and stained with toluidine blue for light microscopic measurements of medial thickness. Thin sections were cut for electron microscopy to determine the proportion of the media occupied by smooth muscle cells. This factor was obtained from cross-sectional photographs by planimetry.

Experiments were rejected if the effective active pressure at \( L_1 \) was less than 100 mm Hg. Out of the 62 vessels which were successfully mounted, results from 13 of these were thus rejected (9 WKY, 4 SHR).

Results

CHARACTERISTICS OF K\(^+\) CONTRACTURES

K\(^+\) Response

Typical responses to activating solution (5 mm Ca\(^{2+}\) in K\(^+\)-Ringer), relaxing solution (EGTA in K\(^+\)-Ringer), and normal Ringer’s solution are shown in Figure 3. The response to activating solution has two parts. During the first, about 80% of final tension is developed within about 10 seconds; in the second the tension rises more slowly to the final value and reaches it after about 1 minute. The response to relaxing solution consists of a transient tension increase (caused by membrane depolarization) followed by a decay to the resting tension within about 1 minute (as the Ca\(^{2+}\) is withdrawn). In Ringer’s solution the vessel normally relaxed to the same resting tension found in relaxing solution. Occasionally, however, toward the end of experiments the relaxation in Ringer’s solution was incomplete, and this was attributed to membrane failure.

NORMALIZATION OF INTERNAL CIRCUMFERENCE

Vessel dimensions were normalized using the resting wall tension-internal circumference curve determined as described above. \( L_{100} \) was defined as the internal circumference corresponding to the point on the fitted exponential curve for which the effective transmural pressure was 100 mm Hg. Thus \( L_{100} = L_{100}/\pi \) is an estimate of the lumen diameter the vessel would have had in situ when relaxed and under a transmural pressure of 100 mm Hg. For reasons given below the experiments described in this paper were performed at an internal circumference \( L_1 = 0.8 L_{100} \), except where stated otherwise.
Phasic spontaneous activity was never observed. Histological examination of the vessels used here showed that all the smooth muscle cells are orientated circumferentially, and therefore that they all contribute to the active tension measured. The resting tension measured arises largely, if not entirely, from the properties of the passive elements in the wall.

Dynamic Stiffness

During the second active response shown in Figure 3 the dynamic stiffness was measured by imposing square wave length changes of amplitude 0.003 L, 0. These were analyzed by using signal averaging techniques. In 11 experiments with WKY vessels the mean value of the dynamic stiffness was found to be 56 ± 6 AT/L, where AT was the active wall tension at L. These small vibrations never produced any drop in tension as has been reported for larger amplitude vibrations.

Graded Responses

The active response was found to be dependent on the concentration of Ca2+ in the K+-Ringer. Figure 4 shows the determined Ca2+ dose-response curves for SHR and WKY vessels. The responses are expressed as a proportion of the response with 5 mM Ca2+. Higher concentrations were not used because this resulted in calcium precipitation in the K+-Ringer. Hansen and Bohr used different buffer systems for K+ solutions containing high Ca2+ concentrations, but found that increasing the Ca2+ concentration above 5 mM resulted in a depression of the response. We also conducted pilot experiments with epinephrine, norepinephrine, and electrical stimulation as Herlihy and Murphy did in their investigation of hog carotid artery. These tests confirmed that a maximal response was given with 5 mM Ca2+. Thus for both WKY and SHR vessels the response to our activating solution has been taken as a measure of the maximal contractile response of the vessel.

COMPARATIVE RESPONSES OF SHR AND WKY VESSELS

As in striated muscle both the active isometric response and the resting tension of smooth muscle are dependent on its length. Figure 5 shows the relationship obtained for three WKY and four SHR first branch vessels. Two points may be noted. First, the resting wall tension-internal circumference relationships of these SHR and WKY vessels are very similar. Second, the SHR vessels produced considerably more active wall tension at any particular internal circumference than the WKY vessels. These points were tested in a larger experiment that included both first and second branch resistance vessels. The details for the
rats used and the experiment plan are shown in Table 1. It will be noted that the SHR had a 52% higher systolic blood pressure and a 21% higher heart-body weight ratio than the WKY. Their age, weight, and sex distribution were similar.

**Resting Wall Tension**

The resting wall tension-internal circumference relation of all vessels was measured as described in Methods. The values of the effective normalized diameter, $l_{100}$, obtained from the exponential curve fitted to the points obtained are shown in Table 2. These indicate that $l_{100}$ is not dependent on whether the vessel was taken from an SHR or WKY. The mean $l_{100}$ value for first branch resistance vessels was 61% larger than that for the second branch vessels. The exponential curve obtained for each vessel was then expressed in the form:

$$T = T_{100} \exp\left(\frac{(L - L_{100})}{L_{100}}/\beta\right),$$

where $T_{100}$ is the resting wall tension at $L_{100}$ and $\beta$ is the proportional change in internal circumference required to change the resting wall tension by a factor $\exp(1)$. The mean values found for $\beta$ are shown in Table 2. There was a wide variation in the values obtained within each group, but there was no indication of any differences between groups.

### Table 1 Characteristics of Rats Used in This Investigation and Experiment Plan

<table>
<thead>
<tr>
<th></th>
<th>SHR</th>
<th>WKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>195 ± 3*</td>
<td>128 ± 3</td>
</tr>
<tr>
<td>Heart/body weight (mg/g)</td>
<td>3.4 ± 0.1*</td>
<td>2.8 ± 0.04</td>
</tr>
<tr>
<td>Age (weeks)</td>
<td>21 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>316 ± 13</td>
<td>314 ± 13</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>83</td>
<td>79</td>
</tr>
<tr>
<td>Resistance vessel type used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st branch</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>2nd branch</td>
<td>7</td>
<td>14</td>
</tr>
</tbody>
</table>

**Active Wall Tension**

The active wall tension-internal circumference curves (Fig. 5) show that for both SHR and WKY vessels the maximum wall tension is obtained at between 0.9 $L_{100}$ and $L_{100}$. In this region the resting wall tension is between 30% and 50% of the active wall tension. Thus, precise active wall tension measurements are to some extent masked here by the resting wall tension. For this reason the active responses were compared at $L_{1}$ = 0.8 $L_{100}$, where the resting wall tension was 10-15% of the active wall tension.

### Table 2 Summary of Vessel Parameters Obtained in This Study

<table>
<thead>
<tr>
<th>First branch resistance vessel</th>
<th>Second branch resistance vessel</th>
<th>P values from t-test*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHR vs. WKY 1st vs. 2nd</td>
<td>SHR vs. WKY 1st and 2nd</td>
</tr>
<tr>
<td>1. Effective normalized diameter, $l_{100}$ (µm)</td>
<td>236 ± 5 (11)</td>
<td>257 ± 9 (15)</td>
</tr>
<tr>
<td>2. Wall tension (mN/mm)</td>
<td>3.0 ± 0.2 (11)</td>
<td>2.5 ± 0.1 (15)</td>
</tr>
<tr>
<td>3. Effective active pressure at $L_{1}$ (mm Hg)</td>
<td>249 ± 16 (11)</td>
<td>199 ± 12 (15)</td>
</tr>
<tr>
<td>4. Wall thickness at $L_{100}$ (µm)</td>
<td>17 ± 2 (11)</td>
<td>13 ± 1 (15)</td>
</tr>
<tr>
<td>5. Wall stress at $L_{100}$ (mN/mm²)</td>
<td>153 ± 8 (11)</td>
<td>148 ± 7 (15)</td>
</tr>
<tr>
<td>6. Smooth muscle cell content (proportion)</td>
<td>0.41 ± 0.02 (2)</td>
<td>0.36 ± 0.06 (2)</td>
</tr>
<tr>
<td>7. Smooth muscle stress (mN/mm²)</td>
<td>373</td>
<td>411</td>
</tr>
<tr>
<td>8. Length constant $\beta$</td>
<td>0.13 ± 0.01 (11)</td>
<td>0.12 ± 0.01 (15)</td>
</tr>
</tbody>
</table>

Values are means ± SE. SHR = spontaneously hypertensive rats; WKY = normotensive Wistar-Kyoto rats. Numbers in parentheses denote number of rats.
* Symbols have the following meanings: + + + , $P < 0.001$; + + , $P < 0.005$; + , $P < 0.02$; -, not significant ($P > 0.05$). Blank spaces indicate that the $t$-test is not applicable.
† Evaluated by the line 5/line 6; mean value only.
Repeated activations at L₁ never showed any potentiation in the response and often showed a cumulative small decline in the response measured. This decline was attributed to a failure of the smooth muscle cells and, as we sought to compare the maximal response of the vessels, we have compared the initial responses of the vessels at L₁. The mean of these responses is shown in Table 2 and in Figure 6. These results show that the SHR vessels are able to contract about 34% more strongly than the corresponding WKY vessels. The second branch resistance vessels in both cases produced less tension than the first branch resistance vessels, but if their contractility is normalized by using Laplace’s equation to determine the pressure against which they would just be able to contract (effective active pressure, Table 2) the difference is less marked.

**Active Wall Stress**

Table 2 also shows the wall thickness measured at L₁₀₀. Here we found that there was no difference between the wall thickness of first and second branch vessels, but that on average the SHR vessels had a 23% greater wall thickness than the WKY vessels. These measurements were used to compute the active wall stress of each vessel (Table 2). There was no significant difference in the active wall stress of SHR and WKY vessels, but in each case the active wall stress of second branch resistance vessels was lower than that of first branch resistance vessels.

The medial thickness and smooth muscle cell content of some of the vessels was determined from histological sections taken from vessels after fixation at L₁. Both the medial thickness and the smooth muscle cell content of the second branch vessels are smaller than those of the first branches. Thus the active force per unit area of smooth muscle cell (on average, 353 mN/mm²) was about the same in all cases. We have not, however, made sufficient measurements to test these results (summarized in Table 2) rigorously, nor have we been able to determine whether the increased active wall tension of the SHR vessels is due to an increased smooth muscle cell content, although our results suggest that this may be the case.

**Discussion**

Previous investigations into the contractile properties of the vasculature of genetic hypertensive rats have included studies of complete vascular beds and also of isolated vessels, although the latter studies have been confined to the aorta and arteries and veins having lumen diameters greater than 500 μm. These studies have, however, given rather conflicting results (see Bohr for a review). Thus helical strips from SHR aorta and femoral artery were found to have lower contractility than their WKY controls. In contrast others have found no differences between the contractile properties of aortic strips from their SHR and WKY. Studies of the pressor response to activation of complete vascular beds indicate, however, that taken as a whole the vascular bed of SHR contracts more strongly than that of WKY. Thus it has seemed that the increased contractility (defined here as the ability to contract against a given transmural pressure) must reside in the smaller vessels. This conclusion is now supported by the major finding of this study, i.e., that the contractility of first and second branch arterial resistance vessels is about 34% higher in SHR than in WKY.

In comparing our results with those obtained from larger vessels it must be remembered that the preparative technique we have used is very different. For the following reasons, however, we consider that our method is inherently less traumatic to the tissue than the conventional method of cutting helical strips. In our technique the medial layer is protected throughout by the internal elastic lamina and the adventitial layer. At no time during dissection or mounting is the vessel stretched beyond about L₁ and, provided that the ends are cleanly cut, the end effects are minimal because of the circumferential orientation of the smooth muscle cells. The responses we measured, when expressed as force per unit smooth muscle cell area (Table 2), are very similar to that found in the media of hog carotid artery (370 mN/mm²). The dynamic active elastic stiffness measured (56 ΔΤₐ/ΔLₐ) is similar to that previously measured in activated smooth muscle (58 ΔΤₐ/ΔLₐ). Last, the “effective active pressure” measured was in excess of the systolic blood pressure of the rats concerned. We therefore believe that the forces we have measured are a good estimate of the maximal in vivo performance of the vessels.

Our finding that the wall thickness of the SHR vessels was about 23% greater than that of the corresponding WKY vessels is in agreement with the findings of other investigators concerning the morphological changes associated with hypertension. Our histological evidence suggests (Table 2) that this increased wall thickness may be associated with an increased smooth muscle cell content, and that it is this which accounts for the increased contractility we found in the SHR vessels. Folkow and his colleagues have suggested, however, that hypertrophy of the arterial wall of SHR could in itself be a primary cause of hypertension if the increased wall thickness encroaches on the lumen. This hypothesis is supported by their findings that the resistance of relaxed vascular beds is
even elevated in 7-month-old SHR. Finch and Haeusler confirmed this but found no differences in the relaxed vascular resistance in 3-month-old rats. Our results (from 5-month-old rats), show no significant difference in the effective lumen diameters between corresponding SHR and WKY vessels. Furthermore, the form of the resting wall tension-internal circumference curve is the same for both WKY and SHR vessels. Therefore our results show no differences in the passive properties of the SHR and WKY vessels we tested which could account for increased vascular resistance.

One of the purposes of investigations concerning the vasculature of hypertensive animals has been to obtain evidence as to whether increased vascular resistance is a primary cause of increased blood pressure or whether it is a secondary effect. Our findings suggest to us, however, that the changes in both the vasculature and blood pressure are secondary effects. The 52% greater systolic blood pressure found in our SHR indicates that their mean blood pressure was about 35% greater than that of the WKY (B. Folkow, personal communication). This may be compared with the 30% greater vessel contractility, the 23% greater wall thickness, and the 21% greater heart-body weight ratio found in the SHR. We are therefore inclined to interpret our results as indicating that both the myocardium and the vasculature have reacted equally to some disturbing influence in the cardiovascular regulatory system. The possible site of this disturbance must for us be a matter of speculation. The evidence of other workers has suggested that the site may be neurogenic, in the smooth muscle cell membrane, or baroreceptors.

All these sites are no doubt involved and, as the systems analysis approach of Guyton and his colleagues indicates, a full understanding of the causes of hypertension requires an understanding of all the many factors involved in the control of the circulation.

Another approach to determining the prime cause of hypertension may be an evolutionary one. It is clear that blood pressure is directly related to the two most important functions of the cardiovascular system, namely, blood flow and the maintenance of capillary pressure. In SHR the cardiac index (and the blood flow index in the superior mesenteric artery) is the same as in WKY. Although the capillary pressure of SHR with established hypertension has not been measured, in genetically hypertensive cats it is not more than 10% greater than that of the normotensive controls. Thus in both genetically hypertensive and normotensive animals the two most important functions of the cardiovascular system are apparently similar. It seems likely, however, that the cardiovascular system has evolved in such a way that the expenditure of energy required to perform these functions is a minimum. It seems likely, however, that the cardiovascular system has evolved in such a way that the expenditure of energy required to perform these functions is a minimum.

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The Influence of the Time Interval between Coronary Artery Occlusion and the Administration of Hyaluronidase on Salvage of Ischemic Myocardium in Dogs

L. David Hillis, Michael C. Fishbein, Eugene Braunwald, and Peter R. Maroko

SUMMARY The purpose of this study was to determine the time interval following coronary artery occlusion during which the administration of hyaluronidase exerts a significant protective effect on injured myocardium. Forty-eight open-chest dogs with coronary artery occlusion were studied. Fourteen were untreated (controls). Hyaluronidase (500 NF units/kg, iv) was administered 20 minutes (12 dogs), 3 hours (8 dogs), 6 hours (8 dogs), or 9 hours (6 dogs) after occlusion. Epicardial electrograms, recorded from 10 to 16 sites on the anterior surface of the left ventricle, were analyzed for creatine phosphokinase (CPK) activity and histological appearance. In all five groups, myocardial CPK depression, histological evidence of the extent of necrosis, and changes in QRS configuration correlated well with one another. In the controls, S-T segment elevation 15 minutes after occlusion (ST15m) correlated with myocardial CPK depression, histological evidence of the extent of necrosis, and changes in QRS configuration. When hyaluronidase was given 20 minutes, 3 hours, or 6 hours after coronary occlusion, myocardial salvage was reflected in significantly less myocardial CPK depression for any given ST15m, less histological evidence of infarction, and less extensive changes in QRS configuration than in the untreated dogs, although there was a progressive reduction in tissue salvage as the time interval between occlusion and drug administration lengthened. Hyaluronidase administered 9 hours after occlusion had no demonstrable effect on the development of myocardial necrosis, suggesting that ischemic injury is totally irreversible by this time.

MYOCARDIAL necrosis following coronary artery occlusion can be limited by certain interventions designed to improve the balance between oxygen supply and demand. Numerous interventions—hemodynamic, metabolic, and pharmacological—have been shown to reduce ischemic injury. In most of these studies the intervention under investigation has been applied either immediately before coronary artery occlusion or shortly thereafter (i.e., 30 minutes after occlusion), at a time when most cells still are reversibly injured. A few observations have been made in which interventions have been applied several hours after occlusion, and a beneficial effect has, in general, been observed. However, a systematic study designed to examine the relative efficacy of an intervention administered at various time intervals after coronary artery occlusion has not been performed.

Hyaluronidase has been shown to limit myocardial ne-
Contractile properties of small arterial resistance vessels in spontaneously hypertensive and normotensive rats.
M J Mulvany and W Halpern

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