Effects of Duration and Severity of Arterial Hypertension and Cardiac Hypertrophy on Coronary Vasodilator Reserve

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SUMMARY. Cardiac hypertrophy is associated with a decrease in coronary reserve. However, factors which may modulate the interaction between myocardial growth and vascular proliferation, such as duration and severity of hypertrophy, have not been evaluated. We measured myocardial perfusion with microspheres in conscious, chronically instrumented Wistar-Kyoto (WKY) and spontaneously hypertensive (SHR) rats at 3, 7, and 15 months of age; and in SHR stroke-prone (SHR-SP) rats at 13-14 months of age. Myocardial perfusion was measured with microspheres in awake rats at rest and during maximal coronary dilation produced by dipyridamole infusion (2.0 mg/kg per min, iv). Arterial pressure was significantly elevated (P < 0.05) in all hypertensive groups (vs. age-matched WKY), both at rest and during dipyridamole infusion. Left ventricular mass in the SHR rats was increased significantly (P ≤ 0.05) by 14%, 28%, and 29% at 3, 7, and 15 months, respectively. Left ventricular mass in the SHR-SP group was increased by 50% (P < 0.05) compared to the 15-month-old WKY. Left ventricular minimal coronary vascular resistance (per gram) was significantly greater (P < 0.05) in SHR at 7 months, and in the SHR-SP group (66% and 60%, respectively). Right ventricular minimal coronary vascular resistance was significantly greater (P < 0.05) in SHR at 7 and 15 months (50%), and in the SHR-SP group (122%), compared to 15-month-old WKY. The results indicate the following: (1) the increase in minimal coronary vascular resistance between SHR and WKY rats was greatest when left ventricular hypertrophy peaked (7 months) and was no longer present after left ventricular hypertrophy had stabilized. (2) In 14-month-old SHR-SP rats, with more severe left ventricular hypertrophy and hypertension, minimal coronary vascular resistance was considerably higher than in SHR of approximately the same age. (3) Long-term arterial hypertension was associated with a higher right ventricular minimal coronary vascular resistance. Resistance appeared to change in proportion to the severity of hypertension, and the changes were independent of the presence of right ventricular hypertrophy. (Circ Res 51: 10-18, 1982)

IT IS generally accepted that cardiac hypertrophy adversely affects the coronary circulation (Holtz et al., 1977; Mueller et al., 1978; O’Keefe et al., 1978; Rembert et al., 1978; Marcus et al., 1979; Breisch et al., 1980; Mittmann et al., 1980; and Bache et al., 1981). Studies of these modulating factors (severity and duration of LVH) are relatively difficult in large laboratory animals; however, the rat, offers several unique advantages. First, because of its short life-span, the age of the animal is known, and effects related to the duration of hypertrophy can be discerned over a significant portion of the animal’s life. Second, there are several rodent models of arterial hypertension available which include the spontaneously hypertensive rat (SHR) (Okamoto and Aoki, 1963) and the spontaneously hypertensive stroke-prone rat (SHR-SP) (Okamoto et al., 1974). These genetic strains are widely used animal models of essential hypertension, which is the most frequent form of left ventricular pressure overload in humans (World Health Organization, 1959, 1962). In this study, we examined coronary vasodilator reserve in the SHR at three stages of LVH: (1) the developing stage at 3 months, (2) peak hypertrophy at seven months, and (3) stable hypertrophy at 15 months of age (Tomanek and Hovanec, 1981). A group of 13- to 14-month-old SHR-SP rats also were studied because hypertension and LVH are more...
severe in this strain than in SHR. Age-matched Wistar-Kyoto (WKY) rats were used as controls; 15-month-old WKY rats were used as controls for the SHR-SP group.

Methods

Two general approaches were used to assess the coronary circulation in rats. Myocardial perfusion was measured by the radioactive microsphere technique. Coronary blood flow velocity was assessed with a pulsed Doppler system.

Microsphere Studies

Age-matched, male WKY and SHR rats were studied at 3, 7, and 15 months of age. A group of male SHR-SP rats (13-14 months old) also were examined. All rats were obtained from the University of Iowa Cardiovascular Center colony and were maintained under identical conditions.

Instrumentation

The rats were anesthetized with sodium pentobarbital (50 mg/kg ip). Arterial catheters (PE10) were placed in the left brachial and femoral arteries. The left ventricle was catheterized retrograde via the right common carotid artery with PE10 tubing. The arterial and left ventricular catheters consisted of a short segment of PE10 tubing, telescoped and glued into a length of PE50 tubing. Only the PE10 segment was intravascular. A venous catheter (PE50) was placed in the right external jugular vein. The catheters were flushed with heparinized saline (200 U/ml). The free ends of the four catheters were then plugged, tunneled subcutaneously to the back of the rat's neck, and exteriorized. After all incisions were closed, the animals were allowed to regain consciousness.

Measurement of Myocardial Perfusion

On the day after instrumentation, regional myocardial perfusion was measured by injections of radioactive microspheres, 8-10 µm in diameter, labeled with one of four nuclides (125I, 51Nb, 85Sr, and 41Sc). Previous studies have shown that, in acute experiments, there is negligible shunting of microspheres—even this small—in the left ventricle (Utley et al., 1974). Prior to use, the microspheres were agitated vigorously on a mechanical shaker for 15 minutes. For each flow determination, approximately 5 X 10⁵ microspheres were injected via the left ventricular catheter. Two reference blood samples were obtained simultaneously from the brachial and femoral arteries at a rate of 0.20 ml/min. The free ends of the left and right halves of the interventricular septum, and the subepicardial and subendocardial halves of the left ventricular free wall. Each sample was weighed to the nearest milligram and placed in a counting tube along with 2 ml of a 1.5% gluteraldehyde solution to preserve the tissue for subsequent counting. Blood from the two reference samples was divided into aliquots of approximately 2 ml and placed in counting tubes. The samples were counted for 10 minutes each in a 3-inch well-type γ counter; output from the counter was recorded on paper tape and processed with a PDP-11 computer. Isotope separation was performed according to standard techniques (Rudolph and Heyman, 1967).

Myocardial perfusion was calculated using the formula:

\[ MP = \frac{C_m \times 100 \times BF_r}{C_r} \]

where \( MP \) = myocardial perfusion (ml/min X 100 g), \( C_m \) = counts/g of myocardium, \( BF_r \) = reference blood flow (the rate of brachial and femoral counts/min for the reference blood samples), and \( C_r \) = the mean of the toal counts in the reference blood samples. Flow determinations were discarded if the activity in the two reference samples differed by 20% or more. This occurred in eight of 243 measurements. The average percent difference in reference sample activities was 6.0 ± 0.1% (mean ± ssm). Coronary vascular resistance was calculated in two ways: (1) the normalized coronary vascular resistance was calculated by dividing the mean arterial pressure by the coronary flow/100 g of tissue (ml/min X 100 g), and (2) the resistances of the whole left and right ventricles were calculated by dividing the mean arterial pressure by the total coronary flows (ml/min) to the left and right ventricles, respectively.

Protocol

Studies on conscious rats were performed on the day following surgery, when the animals were active and had recovered from surgery. The rats were studied while they were unrestrained in an open-top animal cage.

Arterial pressure and heart rate were monitored with an Ailtech MS20 transducer placed at mid-animal level. These parameters were recorded on a direct-writing oscillographic recorder. Blood (0.3 ml) was withdrawn for measurements of blood gases and hematocrit. The withdrawn blood was immediately replaced with an equal volume of strain-matched donor blood.

When the rats appeared to be accustomed to the laboratory setting, baseline hemodynamic parameters were measured. To measure regional myocardial perfusion, an injection of radioactively labeled microspheres was made in the left ventricle.

After the control measurements were made, maximal coronary vasodilation was induced with an infusion of dipyridamole. The dipyridamole was administered, iv at a dose of 2 mg/kg per min for 10 minutes with a Harvard infusion pump. This dose was chosen after preliminary studies indicated that higher doses produced no further significant coronary dilation, regardless of species or age. At the onset of dipyridamole infusion, the arterial pressure decreased, and the heart rate increased. When these parameters had stabilized, and after the required 10 minutes of dipyridamole infusion, all hemodynamic parameters again were measured. Maximal myocardial perfusion then was determined by injection of a second batch of differently labeled radioactive microspheres into the left ventricle. The dipyridamole infusion was continued for 2 minutes after the microspheres were injected.

To accommodate animal-to-animal variability and thus ensure a measurement of maximal myocardial perfusion in each rat, every animal received a second dose of dipyridamole that was at least twice that of the first dose (4-8 mg/kg per min for 10 minutes). Again, after stabilization of blood pressure and heart rate and the required 10-minute infusion period, hemodynamic parameters were measured, and a batch of microspheres that had been labeled with a third radioisotope was injected into the left ventricle. Drug infusion continued for 2 minutes after microsphere injection.

At the conclusion of the experiment, the rats were killed with a lethal dose of sodium pentobarbital intraarterially (ia). The chest was opened and the heart removed. After fat
and great vessels had been trimmed away, the right
and left ventricles were separated. For each animal, right
ventricular weight:body weight and left ventricular
weight:body weight ratios were determined. Subsequently,
the ventricles were divided into five segments as described
in Methods.

Doppler Studies

We have developed a directional pulsed Doppler system
capable of recording phasic and mean coronary blood flow
velocity in the rat (Wangler et al., 1981). This system was
used in this study to examine cardiovascular stability during
microsphere measurements of myocardial perfusion, and to
assess the coronary dilator response to dipyridamole.

Animal Preparation

Rats were anesthetized with methoxyflurane and venti-
lated via an endotracheal tube with a mechanical respirator.
One milliliter of methoxyflurane was vaporized and admin-
istered intermittently as required.

Catheters (PE50) were placed in the left brachial and left
femoral arteries and right external jugular vein. A 40-mm
segment of PE10 tubing, telescoped into a length of PE50
tubing, was placed in the left ventricle via the right carotid
artery; only the PE10 segment was intravascular. The cath-
eters were flushed with heparinized saline (200 U/ml). A
midsternal thoracotomy then was performed, and the Dop-
pler probe was placed over the left anterior descending
coronary artery. However, the rate of withdrawal was twice that used
during this procedure because arterial pressure and heart
rate were being continually monitored from the femoral
tubing, was placed in the left ventricle via the right carotid
artery. Only the PE10 segment was intravascular. The cath-
eters were flushed with heparinized saline (200 U/ml). A
midsternal thoracotomy then was performed, and the Dop-
pler probe was placed over the left anterior descending
coronary artery (LAD), midway between the apex and base
of the heart. Blood (0.3 ml), was withdrawn for measure-
ment of gases and hematocrit, and immediately replaced
with donor blood. Arterial pressure was measured with a
Statham P23 la transducer. Mean and phasic coronary
velocity, systemic blood pressure, and heart rate were re-
corded on a direct-writing oscillographic recorder. A zero
reference recording of coronary velocity was obtained by
occluding the LAD with a metal spatula.

Protocol

To study cardiovascular stability during measurements
of myocardial perfusion, we performed the following ex-
periments in three WKY rats at 7 months of age.

Phasic and mean LAD blood flow velocity, arterial pres-
sure, and heart rate were continuously monitored. Micro-
spheres were injected via the left ventricular catheter. Ref-
ence blood was withdrawn from the brachial catheter at
a rate of 0.40 ml/min, starting before microsphere injection
and continuing for 2 minutes thereafter. After the with-
drawn blood had been replaced, dipyridamole was infused
iv at a rate of 2 mg/kg per min for 10 minutes. Microspheres
were injected into the left ventricle and reference blood was
withdrawn for 2 minutes. Dipyridamole infusion was con-
tinued until the end of the reference withdrawal period.

Only one arterial reference sample could be withdrawn
during this procedure because arterial pressure and heart
rate were being continually monitored from the femoral
artery. However, the rate of withdrawal was twice that used
in the previously described conscious rat study.

In three 7-month-old WKY rats, we compared the inten-
sity of coronary dilation produced by dipyridamole to that
obtained during coronary reactive hyperemia. LAD occlu-
sion for 20 seconds results in a maximum coronary reactive
hyperemic response in the rat (Peters et al., 1981). After a
control, 20-second occlusion, dipyridamole was infused (2
mg/kg per min, iv) for 10 minutes. Additional LAD occlu-
sions (20-second) were performed at various times during
the infusion period.

Statistical Analysis

Comparisons between SHR and age-matched WKY were
based on a two-way analysis of variance. The SHR-SP
group was compared to the 15-month-old WKY and SHR
groups by a one-way analysis of variance. Statistically sig-
ificant differences between group means (P ≤ 0.05) were
tested by the Bonferroni multiple comparison procedure.
All data are expressed as mean ± SEM.

Results

Cardiovascular Stability during Measurements of
Myocardial Perfusion

At rest and during dipyridamole infusion, left ven-
tricular injections of microspheres and simultaneous
arterial reference sample withdrawal for 2 minutes
were associated with less than a 2% change in heart
rate, arterial pressure, and coronary blood flow velo-
city in the left anterior descending coronary artery.

Coronary Vascular Response to Dipyridamole

At all ages, and in all three strains of rats, minimal
coronary vascular resistance, in both the right and left
ventricle, did not differ significantly for the two doses
of dipyridamole (Table 1).

Following dipyridamole infusion at a rate of 2 mg/
kg per min for 10 minutes, coronary blood flow
velocity was increased and a coronary reactive hyper-
emic response was no longer elicited by a 20-second
occlusion of the LAD (Fig. 1).

Baseline Parameters

By 3 months of age, in the SHR, left ventricular
weight:body weight had increased modestly (14%).
By 7 months, the magnitude of hypertrophy had
increased by 28%, compared to age-matched WKY
(Table 2). However, no further hypertrophy occurred
in the SHR from 7 to 15 months of age. SHR-SP rats
had more intense left ventricular hypertrophy (50%
greater left ventricular weight:body weight ratio),
compared to 15-month-old WKY rats.

Table 2

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>SHR</th>
<th>SHR-SP</th>
<th>WKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>14%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>28%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

Ratios of right ventricular weight:body weight were
not significantly different between strains, except for
the increase exhibited by the 15-month-old SHR
group (Table 2).

Blood gases, pH, and hematocrit data from all rats
used in these experiments were within normal physi-
ological limits. For the pooled groups, the mean
values of pH, PO2, PO2, and hematocrit were 7.41 ±
0.01, 94 ± 1 mm Hg, 28 ± 1 mm Hg, and 46 ± 1%,
respectively.

Hemodynamic parameters are presented in Table 3.
In general, heart rates were similar in WKY, SHR,
and SHR-SP at rest and during maximal coronary
dilation. Mean arterial pressure was significantly
decreased by dipyridamole infusion; nevertheless, the
significantly greater blood pressures associated with
the hypertensive strains at rest prevailed following
maximal coronary dilation.
Wangler et al. / Coronary Reserve in Cardiac Hypertrophy

Left Ventricular Perfusion and Coronary Vascular Resistance

Adequate mixing of microspheres in the coronary arteries was demonstrated by two lines of evidence. First, myocardial perfusion in the septum and left ventricular free wall were similar for each animal studied.* Second, the left ventricular posterior and anterior walls also were similar with regard to perfusion. In all comparisons, the values did not vary by more than 10%; this suggests that the microspheres were evenly distributed in the blood flow of two major coronary arteries (LAD and circumflex). Shunting of 10-μm microspheres was also considered in the rat (Tomanek et al., 1980). We found that <1% of the microspheres of this size reached the lung via the pulmonary circulation.

Left ventricular perfusion (ml/min X 100 g) at rest was not significantly different in the hypertensive and normotensive strains, but increased significantly in all groups after infusion of dipyridamole (Table 3). Hypertension and hypertrophy in SHR did not significantly alter the relative proportion of perfusion to the subendocardium and subepicardium at rest (Table 3). However, the relative reduction in subendocardial/subepicardial perfusion decreased in all normotensive and hypertensive groups. The relative reduction in subendocardial perfusion was more marked in each of the normotensive groups.

Resting values of left ventricular coronary vascular resistance were similar for the hypertensive and normotensive strains (Table 4). Maximal coronary dilation consistently resulted in a significant decrease in coronary vascular resistance. During maximal coronary dilation, total resistance (mm Hg/ml·min) in the left ventricle did not differ between the hypertensive and normotensive strains. However, when minimal coronary vascular resistance was corrected for ventricular mass (mm Hg/ml·min X 100 g) the 7-month-old SHR group had a resistance which was 67% greater than its age-matched control. At 15 months of age, this abnormality was no longer present. The SHR-SP group had a minimal resistance that was 60% greater than that of the 15-month-old WKY group and 33% greater than the SHR group at 15 months of age. Although the mean values for minimal coronary resistance tended to increase with age in both strains, linear regression analysis showed that this parameter was not significantly related to age.

Right Ventricular Perfusion and Coronary Vascular Resistance

Right ventricular perfusion under resting conditions is not statistically significant between strains at any given age, and in all cases maximal coronary dilation resulted in a significant increase in right ventricular perfusion (Table 3). Whereas the values for SHR and WKY were similar at 7 and 15 months, in younger (3-month-old) SHR we noted a trend toward higher values, compared to WKY.

Resting coronary vascular resistance in the right ventricle did not differ significantly between the hypertensive and normotensive strains (Table 4). Maximal coronary dilation consistently resulted in a significantly decreased vascular resistance in all groups. Values of total minimal coronary vascular resistance

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* For all groups, the pooled values (mean ± sem) of septal vs. left ventricular free wall perfusion (ml/min X 100 g) were: 480 ± 26 vs. 474 ± 27 (P > 0.05) at rest, and 856 ± 58 vs. 913 ± 23 (P > 0.05) following maximal coronary dilation with dipyridamole.

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**Table 1**

Left and Right Ventricular Coronary Vascular Resistance during the Infusion of Two Different Doses of Dipyridamole

<table>
<thead>
<tr>
<th>Dipyridamole dose (ml/kg per min)</th>
<th>WKY/3 mos</th>
<th>WKY/7 mos</th>
<th>SHR/3 mos</th>
<th>SHR/7 mos</th>
<th>WKY/15 mos</th>
<th>SHR/15 mos</th>
<th>SHR-SP/13-14 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 12</td>
<td>n = 11</td>
<td>n = 10</td>
</tr>
<tr>
<td>Left ventricular coronary vascular resistance [mm Hg/(ml·min X 100 g)]</td>
<td>2</td>
<td>0.10±0.02</td>
<td>0.11±0.01</td>
<td>0.11±0.02</td>
<td>0.16±0.01</td>
<td>0.11±0.01</td>
<td>0.13±0.02</td>
</tr>
<tr>
<td></td>
<td>4-8</td>
<td>0.09±0.01</td>
<td>0.11±0.01</td>
<td>0.11±0.02</td>
<td>0.16±0.02</td>
<td>0.10±0.01</td>
<td>0.12±0.01</td>
</tr>
<tr>
<td>Right ventricular coronary vascular resistance [mm Hg/(ml·min X 100 g)]</td>
<td>2</td>
<td>0.08±0.02</td>
<td>0.08±0.01</td>
<td>0.09±0.02</td>
<td>0.13±0.02</td>
<td>0.09±0.02</td>
<td>0.13±0.02</td>
</tr>
<tr>
<td></td>
<td>4-8</td>
<td>0.07±0.01</td>
<td>0.08±0.01</td>
<td>0.08±0.02</td>
<td>0.12±0.01</td>
<td>0.09±0.01</td>
<td>0.13±0.02</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. In all three rat strains, at all of the ages used in this study, dipyridamole at doses equal to or greater than 2 mg/kg per min produced maximum coronary dilation. WKY = Wistar-Kyoto rat; SHR = spontaneously hypertensive rat; SHR-SP = spontaneously hypertensive stroke-prone rat.

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**Figure 1.** Following dipyridamole infusion at a rate of 2 mg/kg per min, iv, for 10 minutes, a coronary reactive hyperemic response is no longer elicited by a 20-second occlusion of the left anterior descending coronary artery. CV = coronary blood flow velocity.
TABLE 2
Body and Heart Weight Data

<table>
<thead>
<tr>
<th></th>
<th>WKY/3 mos</th>
<th>SHR/3 mos</th>
<th>WKY/7 mos</th>
<th>SHR/7 mos</th>
<th>WKY/15 mos</th>
<th>SHR/15 mos</th>
<th>SHR-SP/13-14 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body wt (g)</strong></td>
<td>254 ± 8</td>
<td>256 ± 6*</td>
<td>328 ± 5</td>
<td>372 ± 7*</td>
<td>410 ± 6</td>
<td>370 ± 10*</td>
<td>385 ± 9</td>
</tr>
<tr>
<td><strong>Left ventricular wt (mg)</strong></td>
<td>621 ± 32</td>
<td>825 ± 40*</td>
<td>786 ± 26</td>
<td>1138 ± 26*</td>
<td>968 ± 27</td>
<td>1115 ± 33*</td>
<td>1365 ± 37†‡</td>
</tr>
<tr>
<td><strong>Left ventricular wt:body wt</strong></td>
<td>2.44 ± 0.08</td>
<td>2.79 ± 0.12*</td>
<td>2.39 ± 0.06</td>
<td>3.06 ± 0.05*</td>
<td>2.36 ± 0.05</td>
<td>3.04 ± 0.09*</td>
<td>3.55 ± 0.08†‡</td>
</tr>
<tr>
<td><strong>Right ventricular wt (mg)</strong></td>
<td>148 ± 7</td>
<td>187 ± 22</td>
<td>174 ± 8</td>
<td>218 ± 4*</td>
<td>223 ± 8</td>
<td>278 ± 15*</td>
<td>224 ± 10‡</td>
</tr>
<tr>
<td><strong>Right ventricular wt:body wt</strong></td>
<td>0.58 ± 0.02</td>
<td>0.63 ± 0.07</td>
<td>0.53 ± 0.03</td>
<td>0.59 ± 0.02</td>
<td>0.54 ± 0.02</td>
<td>0.76 ± 0.05*</td>
<td>0.58 ± 0.02‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. WKY = Wistar-Kyoto rat; SHR = spontaneously hypertensive rat; SHR-SP = spontaneously hypertensive stroke-prone rat.

* P < 0.05 vs. age-matched WKY; † P < 0.05 vs. 15-month-old WKY; ‡ P < 0.05 vs. 15-month-old SHR.

Values (mm Hg/ml-min) during dipyridamole infusion were similar for the age-matched SHR and WKY groups. In contrast, total minimal coronary vascular resistance in the right ventricle of the SHR-SP rat was 128% greater than that found in the 15-month-old WKY group and 82% greater than the mean value for 15-month-old SHR. When minimal coronary vascular resistance was normalized for right ventricular mass (mm Hg/ml-min X 100 g), the 7- and 15-month-old SHR had resistances which were 50% greater than those of their controls, and the SHR-SP group had a minimal resistance which was 122% greater than that of the 15-month-old WKY group and 50% greater than the values obtained from the SHR group at 15 months of age.

**Discussion**

The major findings of this study are as follows. First, significant abnormalities exist in the coronary circulation of SHR and SHR-SP rats. The difference in minimal coronary vascular resistance between SHR and WKY rats was demonstrable at peak LVH (7 months), and was no longer present when LVH had

TABLE 3
Hemodynamics and Myocardial Perfusion

<table>
<thead>
<tr>
<th></th>
<th>WKY/3 mos</th>
<th>SHR/3 mos</th>
<th>WKY/7 mos</th>
<th>SHR/7 mos</th>
<th>WKY/15 mos</th>
<th>SHR/15 mos</th>
<th>SHR-SP/13-14 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>382±16</td>
<td>388±15</td>
<td>365±15</td>
<td>377±16</td>
<td>365±9</td>
<td>410±7*</td>
<td>376±14</td>
</tr>
<tr>
<td><strong>Mean arterial pressure (mm Hg)</strong></td>
<td>365±16</td>
<td>402±17</td>
<td>386±14</td>
<td>411±8*</td>
<td>387±16</td>
<td>409±10</td>
<td>407±8§</td>
</tr>
<tr>
<td><strong>Total right ventricular perfusion (ml/min)</strong></td>
<td>105±3</td>
<td>126±5*</td>
<td>101±5</td>
<td>136±6*</td>
<td>100±2</td>
<td>121±4*</td>
<td>147±5†‡</td>
</tr>
<tr>
<td><strong>Left ventricular perfusion (ml/min X 100 g)</strong></td>
<td>1.49±0.29§</td>
<td>2.50±0.24§</td>
<td>2.06±0.34§</td>
<td>2.16±0.18§</td>
<td>2.14±0.16§</td>
<td>2.45±0.36§</td>
<td>1.88±0.19§</td>
</tr>
<tr>
<td><strong>Right ventricular perfusion (ml/min X 100 g)</strong></td>
<td>348±60</td>
<td>523±68</td>
<td>481±164</td>
<td>352±49</td>
<td>370±68</td>
<td>446±51</td>
<td>382±42</td>
</tr>
<tr>
<td><strong>Total left ventricular perfusion (ml/min)</strong></td>
<td>1018±126§</td>
<td>1469±232§</td>
<td>1183±191</td>
<td>998±78§</td>
<td>964±74§</td>
<td>878±121§</td>
<td>846±89§</td>
</tr>
<tr>
<td><strong>Left ventricular perfusion (ml/min X 100 g)</strong></td>
<td>2.97±0.53</td>
<td>4.96±0.63</td>
<td>3.50±0.87</td>
<td>4.11±0.51</td>
<td>4.02±0.63</td>
<td>4.85±0.59</td>
<td>5.51±0.56</td>
</tr>
<tr>
<td><strong>Left ventricular subendocardial/subepicardial perfusion (ml/min X 100 g)</strong></td>
<td>510±94</td>
<td>621±74</td>
<td>474±112</td>
<td>428±63</td>
<td>441±71</td>
<td>447±42</td>
<td>423±38</td>
</tr>
</tbody>
</table>

The n values are the same as in Table 2. Values are mean ± SEM. MCD = maximum coronary dilatation (dipyridamole). WKY = Wistar-Kyoto rat; SHR = spontaneously hypertensive rat; SHR-SP = spontaneously hypertensive stroke-prone rat.

* P < 0.05 vs. age-matched WKY; † P < 0.05 vs. 15-month-old WKY; ‡ P < 0.05 vs. 15-month-old SHR; § P < 0.05 vs. same group at rest.
The n values are the same as in Table 2. Values are mean ± SEM. MCD = maximum coronary dilation (dipyridamole). WKY = Wistar-Kyoto rat; SHR = spontaneously hypertensive rat; SHR-SP = spontaneously hypertensive stroke-prone rat.

Table 4

<table>
<thead>
<tr>
<th>Right ventricular coronary vascular resistance (mm Hg/ml-min x 100 g)</th>
<th>WKY/3 mos</th>
<th>SHR/3 mos</th>
<th>WKY/7 mos</th>
<th>SHR/7 mos</th>
<th>WKY/15 mos</th>
<th>SHR/15 mos</th>
<th>SHR-SP/13-14 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest MCD</td>
<td>0.39±0.07</td>
<td>0.27±0.04</td>
<td>0.36±0.07</td>
<td>0.44±0.07</td>
<td>0.37±0.06</td>
<td>0.29±0.02</td>
<td>0.44±0.06</td>
</tr>
<tr>
<td>MCD</td>
<td>0.07±0.015</td>
<td>0.08±0.015</td>
<td>0.08±0.015</td>
<td>0.12±0.015</td>
<td>0.08±0.015</td>
<td>0.12±0.0115</td>
<td>0.18±0.0155</td>
</tr>
<tr>
<td>Total right ventricular coronary vascular resistance (mm Hg/ml-min)</td>
<td>269±49</td>
<td>155±27</td>
<td>214±42</td>
<td>208±59</td>
<td>169±32</td>
<td>109±11</td>
<td>204±36</td>
</tr>
<tr>
<td>Rest MCD</td>
<td>48±5§</td>
<td>44±4§</td>
<td>44±9§</td>
<td>54±15§</td>
<td>36±5§</td>
<td>45±6§</td>
<td>82±10§</td>
</tr>
<tr>
<td>MCD</td>
<td>0.28±0.01</td>
<td>0.23±0.03</td>
<td>0.31±0.06</td>
<td>0.36±0.04</td>
<td>0.34±0.07</td>
<td>0.30±0.04</td>
<td>0.37±0.03</td>
</tr>
<tr>
<td>Total left ventricular coronary vascular resistance (mm Hg/ml-min)</td>
<td>48±10</td>
<td>29±4</td>
<td>44±8</td>
<td>34±4</td>
<td>37±8</td>
<td>28±44</td>
<td>29±3</td>
</tr>
<tr>
<td>Rest MCD</td>
<td>13±15§</td>
<td>13±15§</td>
<td>13±25§</td>
<td>14±15§</td>
<td>11±15§</td>
<td>12±15§</td>
<td>13±15§</td>
</tr>
</tbody>
</table>

Second, long-term arterial hypertension is associated with an increase in right ventricular minimal coronary vascular resistance. Resistance appeared to change in proportion to the severity of hypertension, and the changes were independent of the presence of right ventricular hypertrophy.

The advantages in the design of this study are several. First, conscious rats were studied, thus alleviating the effects of anesthesia and acute surgical trauma. Second, the rat as an experimental model offers a number of advantages. The development of left ventricular hypertrophy in the SHR has been shown to consist of several discrete stages which encompass a significant portion of the animal's life-span (14 months).

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combination, these studies strongly support our contention that dipyridamole produced maximum coronary dilation.

A second potentially limiting factor in this study involves the use of left ventricular injections of microspheres for measurements of myocardial perfusion. However, cardiovascular stability was assured when it was shown that left ventricular infusion of $5 \times 10^5$ microspheres (9 μm), coupled with reference sample withdrawal for 2 minutes, had minimal effect on heart rate, arterial pressure, or phasic and mean coronary blood flow velocity. Similar results were obtained at rest and during maximal coronary dilation. Left ventricular injections of microspheres may pose an additional question related to the adequacy of mixing. However, three observations attest to the adequacy of this route of injection: (1) based on the 219 measurements of myocardial perfusion in this study, the average percent difference in the two reference sample activities was 6%, (2) the perfusion of the septum and that of the left ventricular free wall were nearly identical,* and (3) the perfusion of the posterior and that of the anterior walls of the left ventricle were also nearly identical. Therefore, microspheres concentration was uniform throughout the coronary arteries.

The remainder of this discussion will focus on three areas: the effects of cardiac hypertrophy on coronary reserve, the effects of time on the interaction between coronary vascular growth and cardiac hypertrophy, and the effects of arterial hypertension on coronary reserve.

Numerous studies have shown that cardiac hypertrophy is associated with a decrement in coronary blood flow reserve (Marchetti et al., 1973; Holtz et al., 1977; Mueller et al., 1978; O'Keefe et al., 1978; Rembert et al., 1978; Breish et al., 1980; Mittmann et al., 1980; Tomanek et al., 1980; Bach et al., 1981). However, most experimental models of cardiac hypertrophy employ hypertension to induce hypertrophy. Therefore, the observed effects of cardiac hypertrophy are difficult to dissociate from those resulting from arterial hypertension. There are a few studies which have examined the effects of cardiac hypertrophy in the absence of arterial hypertension. Murray et al. (1981) produced right ventricular hypertrophy in dogs by banding the pulmonary artery. Despite normal aortic perfusion pressure, right ventricular hypertrophy was characterized by a reduction in maximum coronary dilator capacity. These results suggest that cardiac hypertrophy, independent of arterial hypertension, can act to decrease the reserve capacity of the coronary bed.

There is evidence that neovascularization at the capillary level occurs during cardiac hypertrophy (Arai et al., 1968; Liunquist and Unge, 1972; Bishop and Melsen, 1976; Lund and Tomanek, 1978). However, this vascular growth is inadequate because capillary density is reduced during cardiac enlargement (Shipley et al., 1937; Rakusan, 1971; Henquell et al., 1978; Lund and Tomanek, 1978; Murray et al., 1978; Tomanek et al., 1979; Breisch et al., 1980). If the proliferative capacity of the arteriolar bed is similarly inadequate, then the cross-sectional areas of these vascular beds would decrease (per unit cardiac mass), and this would be manifested as an increased minimal coronary vascular resistance (MCVR). The results of this study suggest that time has an effect on the interaction between the coronary bed and cardiac hypertrophy. Minimal coronary vascular resistance was shown to increase during peak LVH (7-month-old SHR). However, left ventricular minimal coronary vascular resistance was normal in the 15-month-old SHR; this occurred following a stable period of moderate hypertrophy from 7 to 15 months of age. Tomanek and Hovanec (1981) have shown that the significant decrement in capillary density which is present in the 7-month-old SHR is normalized by 15 months of age. If the arterial vasculature expands in proportion to the ventricular mass during the period of stabilized hypertrophy, then the return of minimal coronary vascular resistance to normal (WKY) values is not so surprising. Under these conditions, one might expect total MCVR to decline in SHR between 7 and 15 months. This trend, though not statistically significant, is evident in our data. Thus, it is suggested that the extent of the arterial bed plays a role in the changes observed in minimal vascular resistance. In summary, we suggest that (1) as hypertrophy peaks, vascular growth is inadequate and MCVR increases, and (2) with stabilized hypertrophy, vascular growth continues and with time (an 8-month period) is sufficient to offset the decreased MCVR characteristic of peak hypertrophy. Importantly, this anatomical adaptation would appear to offset the effects of arterial hypertension which continues throughout the life of SHR.

In contrast to the modulating effects of cardiac hypertrophy noted in the left ventricle, the vascular changes which we found in the right ventricle suggest the influence of yet another factor to which the coronary bed is sensitive. Right ventricular minimal coronary vascular resistance was significantly elevated in the 7-month-old SHR and in the SHR-SP groups, despite the absence of right ventricular hypertrophy. These findings would implicate a structural alteration of the coronary vasculature, associated with arterial hypertension; supporting evidence can be found in other studies. Folkow et al. (1970a; 1970b) have shown that medial hypertrophy of the arteriolar wall does occur in skeletal muscle as a result of arterial hypertension. A study by Yamori et al. (1979) concerning the geometry of the coronary resistance vessels in SHR-SP rats, suggests that significant increases in wall-to-lumen ratios occur. Noresson et al. (1977) have noted that in SHR rats there exists an increased resistance to coronary flow during maximum vasodilation, in combination with an increased maximal constrictor response. Considered together, these findings suggest that the coronary resistance vessels, when

* See footnote page 13.
subjected to arterial hypertension, are remodeled so that an increased medial thickness limits maximum vasodilation and accentuates maximum constrictor responses. Bhan et al. (1978) have reported hyperplastic lesions in epicardial and small intramyocardial arteries of rats subjected to renovascular hypertension for 1–4 weeks; they also noted that the severity of the vascular lesions appeared to be related to the severity of hypertension.

In our study, the SHR-SP group had a right ventricular minimal coronary vascular resistance that was significantly greater than that associated with the SHR rats. Therefore, the magnitude of the changes which occur in the coronary bed of the right ventricle appear to be related to the severity of hypertension. This raises the question: why do the responses of the right and left ventricles differ? The major difference between the two ventricles is the gradual development of hypertrophy in the left ventricle. As suggested by our data, vascular growth probably is inadequate during the development of LVH. However, hypertrophy may indeed serve as a stimulus for vascular growth which eventually, during stabilized hypertrophy, compensates for the earlier growth of myocardial mass. In contrast, the right ventricle is subjected to hypertensive levels of blood pressure but not to the stimulus for hypertrophy. Under these conditions, minimal right ventricular coronary vascular resistance might be expected to increase as hypertension develops. Our data support this contention, as MCVR in the right ventricle (adjusted for mass) increased significantly in SHR at 7 months and remained elevated at 15 months. Total right MCVR showed the same trend but did not attain statistical significance, except in the SHR-SP group which demonstrated more markedly elevated blood pressure. Thus, the magnitude of the hypertension may have been a factor in the elevated total RVCVR in that group.

In summary, long-term arterial hypertension and developing LVH were associated with decreased coronary dilator capacity. After the hypertrophying process had stabilized, this abnormality no longer existed, despite persisting hypertension. When arterial hypertension and LVH were more severe, the coronary dilator response was even more depressed. Long-term arterial hypertension, in the absence of right ventricular hypertrophy, was associated with decreased coronary dilator capacity in the right ventricle. Furthermore, this abnormality appeared to be proportional to the severity of the hypertension.

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R D Wangler, K G Peters, M L Marcus and R J Tomanek

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